

MEDICINE

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General Medicine, Neurology and Pediatrics

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DIABETES MELLITUS

● The concise new book combines a discussion of wide clinical experiences with a critical review of all that is valid and important in the extensive literature of carbohydrate metabolism in health and disease

THE AUTHORS

Zolton T. Wirtschafter, M.D., *Clinician in charge Clinic for Diabetes Department of Medicine Mount Sinai Hospital Cleveland Clinical Instructor in Medicine Western Reserve University Cleveland and*
Morton Korenberg, M.D., *Montreal*

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AN EXPLANATION TO SUBSCRIBERS

Readers of this and subsequent issues of this Journal may observe that the pages are somewhat altered in appearance. What is known as the format has been changed. The Journal is now printed on type known as 10-point on a 12-point body, and the type-page is now 29 picas wide and 47 picas long. (A pica is one-sixth of an inch; a point is one-seventy-second of an inch.)

The reason for the change is this: An acute shortage of paper is about to develop. Paper will be increasingly hard to get and it may come to rationing. In the latter case those who have already made some effort to save paper will doubtless receive more consideration than those who have not.

The new format will permit more words to be printed on fewer pages, without loss of legibility, and without curtailment of the amount of material published. The same amount will be printed on fewer pages—that is all. Issues will be thinner but—to repeat in order to emphasize—just as much material will be published in each volume as has hitherto been published.

In brief, then, the change

1. Tends to forestall a threatened break in the continuity of publication of scientific material, or a curtailment of the amount published.

2. It is a way to assist in the general problem of national defense,

3. It tends to forestall, delay, or minimize a possible rise in price. Labor and materials are going up. Saving paper partly neutralizes the effect.

Finally, some pages in this issue may be printed in the old format. This is merely because these pages happened to be already set in type when the change was determined upon.

INFECTIONS WITH THE VIRUS OF LYMPHOCYTIC CHORIO-MENINGITIS

THOMAS W. FARMER AND CHARLES A. JANEWAY¹

From the Medical Clinic of the Peter Bent Brigham Hospital and the Departments of Medicine and Bacteriology and Immunology, Harvard Medical School, Boston

I INTRODUCTION.

In 1925 Wallgren (1, 2, 3) described a clinical picture, which he named 'acute aseptic meningitis'. Each of the cases which he presented fulfilled the following criteria for a clinical diagnosis. There was an acute onset of a febrile illness with symptoms of meningeal irritation. The cerebrospinal fluid revealed a lymphocytic reaction and was sterile on culture. There was no evidence of a septic focus of infection, nor of a traumatic injury or of an exposure to any contagious disease producing a lymphocytic reaction in the cerebrospinal fluid. After a short illness each patient recovered completely without complications. The etiology of this symptom-complex was unknown. However a number of diseases of known etiology, which produced mononuclear reactions in the cerebrospinal fluid were recognized. Syphilitic meningitis and tuberculous meningitis were separate entities. Infections of the middle ear, the sinuses and the mastoids were known to result occasionally in an aseptic meningitis. Virus diseases of the central nervous system (encephalitis and anterior poliomyelitis) had been described. Acute aseptic meningitis was a syndrome distinct from these known illnesses.

During the next few years a considerable number of cases fulfilling Wallgren's criteria were reported under such titles as "aseptic meningitis," "meningitis serosa," and pseudo-tuberculous meningitis (4, 5, 6, 7, 8, 9, 10). As subsequent research has demonstrated these cases did not constitute a single disease entity, but were a group of diseases producing a definite clinical picture in man.

A few of the etiological agents producing the clinical picture of acute aseptic meningitis have been discovered during the past seven years. Of these the virus of lymphocytic choriomeningitis first isolated in 1934 (11), has been studied most widely. Several related viruses producing a somewhat similar picture subsequently have been isolated. These are the virus of pseudo-lymphocytic choriomeningitis and the virus of *la maladie des porchers*. However these known viruses are the cause of only about one-third of the cases of acute aseptic meningitis. In the other two-thirds, no etiological diagnosis is possible at the

¹ Part of the expense of this work was defrayed by a grant from the Proctor Fund for the study of Chronic Disease, Harvard University.

present time. These cases may be described temporarily as acute aseptic meningitis of unknown etiology.

In this review a detailed exposition of the rôle of the virus of lymphocytic choriomeningitis in human disease will be presented. We must acknowledge our debt to several previous reviews of the subject at this point, since they have served directly or indirectly as the source of much useful material (12, 13, 14, 15, 16).

II. THE VIRUS OF LYMPHOCYTIC CHORIOMENINGITIS IN HUMAN DISEASE

A. History

In 1934 Armstrong and Lillie (11) described the isolation of a new virus. This agent was encountered in the transmission from monkey to monkey of infectious material, originally derived from a fatal case of St. Louis encephalitis. Because of the pathological picture produced in monkeys and mice, it was named the virus

TABLE 1

Clinical pictures produced by the virus of lymphocytic choriomeningitis

1	Lymphocytic choriomeningitis Meningeal form
2	Lymphocytic choriomeningitis Encephalomyelitic form
3	Non-meningeal form Non-nervous system infection Systemic infection Grippal infection
3a	Inapparent infection Sub-clinical infection

of lymphocytic choriomeningitis. In the following year, Traub (17) described a virus which produced the same clinical picture in white mice as the virus of Armstrong and Lillie. This virus was carried by apparently healthy mice and was activated by the intracerebral injection of foreign material.

The rôle of the virus of lymphocytic choriomeningitis in human disease was first established by Rivers and Scott in 1935 (18). They studied two patients with the clinical picture of acute aseptic meningitis. From the cerebrospinal fluid of each patient a virus was isolated, which was shown to be serologically identical with the two strains of virus previously isolated by Armstrong and Traub.

B. Terminology

The term 'lymphocytic choriomeningitis' has been used to designate a form of meningitis in man produced by a specific virus. Further investigation has shown that this virus also produces other syndromes. In a few patients, infec-

tion has resulted in the clinical picture of encephalomyelitis. In others a systemic infection without meningitis has been observed. In addition, asymptomatic infection with this virus probably occurs in numerous instances. These various clinical pictures and the synonyms which have been used to describe them are listed in Table 1.

C Distribution

1 Frequency A total of thirty-five proved cases of the meningeal form of lymphocytic choriomeningitis have been reported (16,² 19, 20). This includes three cases of the encephalomyelitic form. The apparent rarity of these forms of infection is due in part to the difficulty of proving the diagnosis. Immunological studies suggest that cases of systemic infection and of inapparent infection without meningitis are quite common. Approximately 11 per cent of 2,000 sera tested (16) contained neutralizing antibodies against this virus.

2 Seasonal incidence Among thirty-three proved cases of lymphocytic choriomeningitis reviewed by Armstrong (16), most of the illnesses occurred during the spring and fall months. Cases were also reported throughout the winter months, but no proved case occurred in July or August.

3 Geographical distribution The virus of lymphocytic choriomeningitis has been isolated in widely separated portions of the United States (11, 17, 21, 22, 23, 24, 25, 26), in England (27, 28), in France (29), and in Japan (30). The evidence suggests that this virus is world-wide in its distribution among human beings and also among mice.

4 Susceptibility in man *Age* Lymphocytic choriomeningitis occurs most often between the ages of 15 and 40 years, although cases in children and elderly individuals have been described. *Race* The virus seems to attack without racial discrimination. In the United States, the frequency of lymphocytic choriomeningitis among whites and negroes has been roughly proportional to the representation of the two races in the population. *Occupation* With the exception of infections among research workers with the virus, this is not an occupational disease.

D The clinical pictures produced in man

It has been known for the past seven years that the virus of lymphocytic choriomeningitis produces a meningeal reaction in man. However, meningitis is only one episode in a systemic infection. When this virus reaches the blood stream, the patient may develop any one of three different clinical pictures: the meningeal form, the encephalomyelitic form, or the non-meningeal form of infection (13). The clinical and experimental observations contributing to the delineation of these various forms of infection will be presented. These data will be summarized in a single outline of the clinical picture of the disease in man.

1 Meningeal form In 1935 Rivers and Scott (18, 23) described the first two cases of human infection with the virus of lymphocytic choriomeningitis. Both of these patients developed febrile illnesses characterized by headache, vomiting,

² For complete list of the first thirty-three cases, see Armstrong (16), Table I, pp. 49-50.

and stiff neck. Lumbar punctures revealed spinal fluids with 720 and 1700 cells per cubic millimeter, nearly all of which were lymphocytes. The patients recovered without any complications.

In 1938 Baird and Rivers (31) reviewed all the cases of lymphocytic choriomeningitis reported in the literature (twenty-three cases). They contrasted the symptoms found in these cases with those in a group of patients who had had acute aseptic meningitis of unknown etiology (eighteen cases). The only significant difference between the clinical pictures in these two groups of cases related to the prodromal symptoms. Of the twenty-three proved virus cases, sixteen gave a history of an influenza-like precursory illness, which lasted from one to three weeks before the onset of meningitis. These early symptoms in-

E. A. PBBH LYMPHOCYTIC CHORIOMENINGITIS

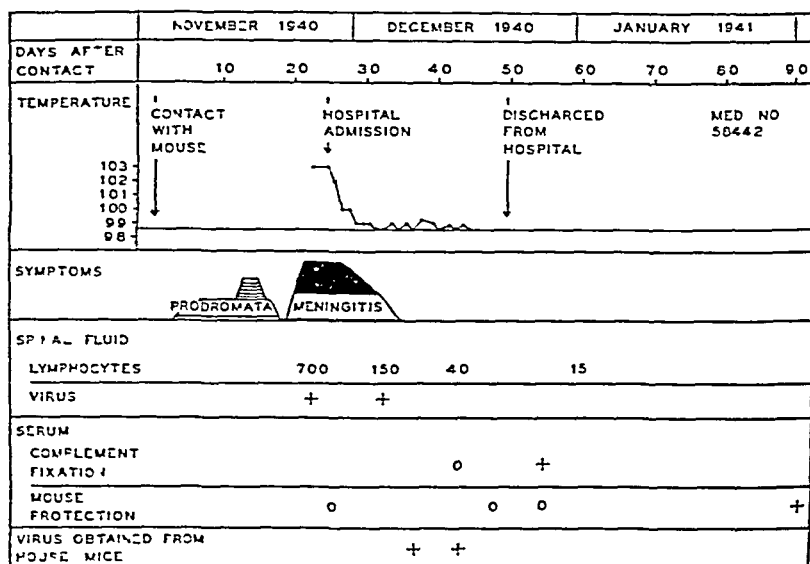


FIG 1 COURSE AND ESSENTIAL LABORATORY DATA IN A CASE OF SPONTANEOUS LYMPHOCYTIC CHORIOMENINGITIS, MENINGEAL FORM
(Authors' case)

cluded malaise, generalized pains, headache, upper respiratory infection, and fever. In contrast with this group, only three of the eighteen cases of unknown etiology gave a history of a prodromal illness before the onset of meningitis.

(a) *Spontaneous infection, case report* The clinical picture of lymphocytic choriomeningitis is best illustrated by the following case history of a patient studied on the Medical Service of the Peter Bent Brigham Hospital, Boston, Mass. In this patient the authors were able to elicit a definite history of the mouse contact, which probably initiated her infection. The virus of lymphocytic choriomeningitis was isolated from her spinal fluid. Grey mice trapped at her home were carrying the same virus. The incubation period from the time of mouse contact to the development of meningitis was twenty days. A febrile,

prodromal illness with a remission before the onset of meningitis occurred. The essential data of this patient's illness are presented graphically in Figure 1.

Case history E. A. (P.B.B.H. Medical No. 58442) is an intelligent, 21-year-old, single negroess who was studying cosmetology in Boston at the time of this illness. She entered the hospital on November 27, 1940, with the complaints of drowsiness and fever of 12 days' duration, and of headache and vomiting of 4 days' duration.

Mouse contact On November 2 she removed a dead mouse from a spring trap. This was the first and only time that she ever touched a mouse in her life. The neck of the mouse had been broken by the trap, but no blood was noticed. Intrigued by this male mouse, she showed it to her uncle. He saw her examining the mouse and urged her to throw it away. "It won't hurt me, it's dead," she said.

Prodromata (first phase of the illness) From November 5 to 8 she felt listless but otherwise well. On November 8 she went home for the weekend. Upon her arrival, her mother asked "What is the matter with you? You look tired, as if you had a fever." Except for this slight fatigue the patient felt well. She returned to school from November 12 to 14.

On the morning of November 15, when she got out of bed she felt "light-headed." She saw "red spots" before her eyes, then "things began to turn black." Upon returning to bed, she felt better. She did not have vertigo, nor did she faint. After eating some soup, she felt nauseated, but did not vomit. Each time that she got out of bed during the day, she had similar spells of light-headedness. This illness prevented her from attending school. She had no chilly sensations at this time.

On November 16, she got out of bed and had another light-headed spell. She visited her physician, who found that her temperature was 101°F (orally). At this time she weighed 107 pounds, whereas one month previously she had weighed 115 pounds. She remained in bed for the next three days. With the exception of mild lethargy, she felt quite well. She ate solid foods with no nausea or vomiting. She had no headache or vertigo. Her temperature was not taken.

On November 20 she returned to school for three days. Her teacher urged her to go home. "I did feel flushed, warm, and tired," she said, "but I would not give up, for I felt well enough to continue my work."

Meningitis (second phase of the illness) She awakened on the morning of November 22 with a slight frontal, bilateral headache, which recurred during the day. She also noted the onset of mild backache. As she was finishing her work of hairdressing in the afternoon, her "hands shook" and her "knees knocked with nervousness." She returned home and slept for an hour, after which she ate heartily. In the evening, stiffness in her neck developed, so that her chin could not touch her chest. She had no respiratory or gastro-intestinal symptoms. The onset of the meningitis was twenty days after contact with the mouse.

On November 23 she was forced to remain in bed with the following symptoms:

- 1 Frontal and temporal, bilateral headache. The headache was mild when she lay down, but throbbed incessantly upon sitting up.
- 2 Stiff neck. The stiffness of the neck increased.
- 3 Lightheaded spells upon trying to get out of bed.
- 4 Nausea and vomiting. She vomited whenever she was forced to take food or medicine. The vomitus did not contain blood.
- 5 Chilly sensations, but no shaking chills.
- 6 Drowsiness. Her lethargy increased so that she slept most of the day and night.
- 7 Loss of appetite.
- 8 Moderate lumbar backache.

During the next two days, she vomited several times a day. Headache, drowsiness, stiff neck, lightheadedness, and chilly sensations persisted. Her bowels did not move. On November 25 her physician visited her. He found her temperature to be 103°F (orally). On the following day she vomited once, and her symptoms persisted. In addition, she first noted that day light hurt her eyes.

On November 27 her headache decreased in severity and she did not vomit. Her neck felt less stiff. However, she was quite drowsy, weak, and feverish with marked photophobia. Upon returning from the bathroom, she fainted, and had to be carried to her bed. On this account, she was admitted to the hospital.

Physical examination Upon admission the patient's temperature was 102°F (rectally), pulse 95, and respirations 20. She lay in bed with her head under the pillow and with the shades drawn, in no apparent discomfort. Upon sitting up, she rapidly became weak. The skin of the extensor surfaces of both thighs, both lower legs, and both upper arms was dry and scaly, in contrast to the fine-textured skin of the remainder of her body. There was no lymphadenopathy. On the posterior buccal mucosa were small white patches of necrotic tissue. There was no exudate on the tonsils or oro-pharynx. The examination of the heart, lungs, and abdomen was negative.

Neurological examination She was quite coherent, in spite of mild drowsiness. Photophobia was marked. Otherwise the cranial nerves were normal, and there were no changes in the optic fundi. There was definite, slight nuchal rigidity. Kernig's sign and Brudzinski's sign were absent. Motor power and sensation were normal. The biceps and triceps reflexes were equal and active bilaterally. Both knee jerks were hypoactive, and could be obtained only by reinforcement. The ankle jerks were equal and active. The abdominal reflexes were active bilaterally. There were no positive Babinski reflexes.

TABLE 2

*The cerebrospinal fluid findings in patient E. A.**

DATE	INITIAL PRESSURE	NUMBER OF LYMPHOCYTES	PROTEIN	SUGAR
	<i>mm CSF</i>	<i>per cu mm</i>	<i>mgs/100 cc</i>	<i>mgs/100 cc</i>
11-29-40	160	700	155	55
12- 5-40	100	150	53	64
12-15-40	90	40	76	
12-19-40	80	25	46	
1- 2-41	150	15	40	65

* The Wassermann and Hinton tests were negative. The colloidal gold curve on November 29, 1940, was 2222344000, on December 19, 1940, it was 0011000000. No organisms were found in stained smears. Cultures of the fluid were negative.

Course and spinal fluid findings Shortly after admission the patient's headache, nausea, lightheadedness, and vomiting all ceased. However, her drowsiness increased. Photophobia and slight nuchal rigidity persisted. She had no appetite. Her temperature varied from 102° to 104°F (rectally) during the first two hospital days.

A lumbar puncture was performed on November 29 (Table 2). This revealed opalescent fluid under normal pressure, with 700 lymphocytes per cu mm and no polynuclear or red blood cells. The protein content was increased to 155 mgs per 100 cc, while the sugar remained normal. The colloidal gold curve showed a slight midzone rise. In spite of the positive spinal fluid findings, the patient appeared well and had few complaints.

On November 30 her temperature fell to 99.5°F (rectally), and her pulse was 70. She felt well with the exception of slight stiffness of the neck, poor appetite, and weakness. Both knee jerks remained hypoactive.

By December 5 the stiff neck and drowsiness had disappeared. Her temperature varied from 99.5° to 97.0°F (orally). She now weighed only 99 pounds, but her appetite was improving. The right knee jerk returned to normal vigor, but the left knee jerk could be elicited only by reinforcement. Definite photophobia persisted. A lumbar puncture on this day revealed clear fluid, under normal pressure with 150 lymphocytes per cu mm. The spinal fluid protein content had fallen to 53 mgs per 100 cc, and the sugar content was 64 mgs per 100 cc (Table 2).

Contalescence (third phase of illness) On December 10 the patient was free of all symptoms including photophobia. The knee jerks were active and equal bilaterally. However her temperature continued to rise each evening to 99.5°F (orally) during the following week. By December 15 the spinal fluid cell count fell to 40 lymphocytes per cu mm. During the next few days the dry, scaly skin of both legs began to peel. On December 19 there were only 25 lymphocytes in the spinal fluid and the patient's temperature was normal throughout the day. She was allowed to get out of bed, and she was discharged from the hospital on December 22, which was her 26th hospital day.

During the next ten days at home she remained in bed most of the time but felt perfectly well. On January 2, 1941, she returned to the hospital for study. The skin of her legs was soft and smooth. Neurological examination was completely negative. Lumbar puncture revealed clear fluid under normal pressure with 15 lymphocytes per cu mm. In January she took a month's vacation, during which time she regained the 20 pounds lost during her illness. She returned to school and has remained well for the past ten months.

Blood (November 27, 1940) The red blood cells were 4,500,000. The hemoglobin was 82 per cent (Sahli), and the hematocrit 45 per cent. There was a 2 mm fall in one hour in the sedimentation rate. The white blood cells were 9,000, with 74 per cent neutrophils, 22 per cent lymphocytes, and 4 per cent monocytes. The red blood cell count increased gradually to 6,500,000 on December 15 and then fell to 5,000,000 on December 20. Of the sedimentation rates repeated on December 1, 9, and 20, each revealed a fall of 4 mm in one hour. The white blood cells varied from 8,500 to 12,000 with no change in the differential count. Blood cultures were negative. Typhoid, paratyphoid, *supestifer*, and sheep cell agglutination tests were all negative. Blood Hinton and Wassermann tests were negative.

Urine Negative

*Isolation of the virus*³ The virus of lymphocytic choriomeningitis was isolated from two specimens of spinal fluid removed from the patient on November 29 and on December 5. This strain was shown to be serologically identical with a standard strain of the virus.

Development of antibodies Sera drawn from the patient on December 19 and 28 were tested for the presence of complement-fixing antibodies.⁴ On December 19 no antibodies were demonstrable in her serum but by December 28 (five weeks after the onset of meningitis) she had developed specific, complement-fixing antibodies in her serum. Neutralizing antibodies were first demonstrable in the patient's serum on February 3, 1941, two months after the onset of meningitis.⁵

*Isolation of the virus from grey mice trapped at the patient's home*⁵ The virus of lymphocytic choriomeningitis was isolated from 5 of 10 grey mice trapped at the patient's home. This virus strain was serologically identical with the one obtained from the patient's cerebrospinal fluid and also with a standard strain of choriomeningitis virus.

Case summary These studies suggest that the patient was infected with the virus on November 2 when she removed a dead mouse from a trap at her home. A definite precursory illness followed this mouse contact. After a remission of symptoms, meningitis developed. The incubation period from the time of mouse contact to the development of meningitis was twenty days. These observations concerning the early clinical course of lymphocytic choriomeningitis are supported by experimental studies.

(b) *Experimental infection* Lépine, Mollaret, and Kleis (32) have shown that subcutaneous inoculation into human beings of a mouse-brain emulsion of lymphocytic choriomeningitis virus produces a febrile illness which is followed in one half of the cases by meningitis. The clinical findings in one of these experi-

³ See appendix.

⁴ These sera were sent to Dr. L. T. Webster, Rockefeller Institute for Medical Research, New York City, who tested the sera for the presence of complement-fixing antibodies.

⁵ See Appendix.

mental cases of lymphocytic choriomeningitis is presented graphically in Figure 2 (13)

Case history B A received a subcutaneous injection of 2 cc of an emulsion of virus-infected, mouse brain, and in 36 hours he developed a fever. During the next fortnight there were two waves of fever. In this prodromal period the virus was isolated from his blood. The white blood cell count revealed a leukopenia of 2100 cells per cu mm. On the eighteenth day after inoculation, the patient developed headache, stiff neck, and fever. At this time, lumbar puncture revealed a slightly cloudy spinal fluid containing 700 lymphocytes per cu mm. From this fluid the virus was isolated. After recovery, circulating antibodies against this virus developed in his blood.

B A EXPERIMENTAL LYMPHO-CHORIOMENINGITIS KREIS

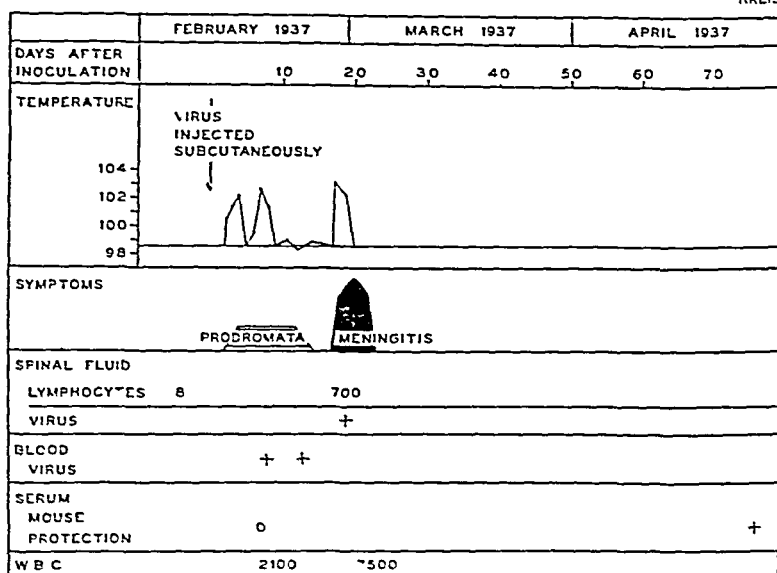


FIG 2 COURSE AND ESSENTIAL LABORATORY DATA IN A CASE OF EXPERIMENTAL LYMPHOCYTIC CHORIOMENINGITIS, MENINGEAL FORM

Patient was inoculated subcutaneously with 2 cc of an emulsion of infected mouse brain (After Kreis (13))

This clinical picture is nearly identical with that described in the patient E. A. When the virus was injected into human beings there was a febrile, prodromal illness of two or three weeks, during which the virus was constantly present in the blood stream. Most of these experimental cases developed gripe-like symptoms with prostration at the height of the fever. Usually two or three febrile waves alternated with periods of normal temperature. One case developed cough and bronchitis during his early illness. In other patients, fever was the only evidence of infection at this period. Following a remission of fever, meningitis developed, and the virus appeared in the spinal fluid. The incubation period from the time of inoculation to the development of fever was one-and-a-half to three days, whereas the period from the time of inoculation to the develop-

ment of meningitis was 15 to 21 days. Neutralizing antibodies developed in the blood of these patients after recovery.

(c) *Laboratory infection* The description by Lépine and Sautter (33) of an accidental laboratory infection presents further details of the clinical picture of lymphocytic choriomeningitis. A chart of the illness of the patient V Sautter, is presented in Figure 3.

Portal of entry of the virus On March 29, 1938, V S, a 28-year-old research worker, was preparing a complement-fixing antigen from the organs of a guinea pig with lymphocytic choriomeningitis. While she was grinding the virulent organs in a mortar with powdered glass, a small fragment of the sharp-edged glass lodged in her conjunctiva. After this

VS LYMPHOCYTIC CHORIOMENINGITIS AN ACCIDENTAL INOCULATION

LÉPINE AND SAUTTER

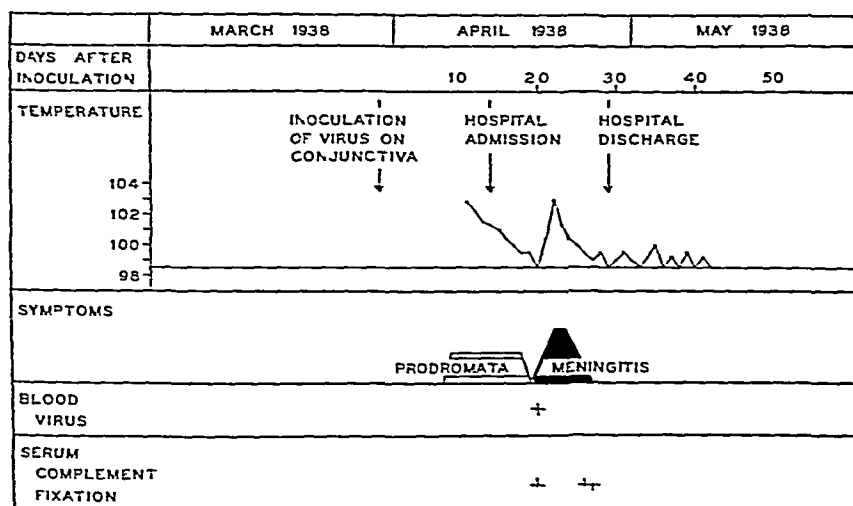


FIG 3 COURSE AND ESSENTIAL LABORATORY DATA IN A CASE OF ACCIDENTAL LABORATORY INFECTION WITH THE VIRUS OF LYMPHOCYTIC CHORIOMENINGITIS

Patient was grinding organs of infected guinea pig and a fragment of powdered glass from the material lodged in her conjunctiva. (After Lépine and Sautter (33))

accident a few drops of a 2 per cent solution of argyrol were instilled into the conjunctival sac. However, it is probable that the imperceptible conjunctival lesion caused by the fragment of glass was the portal of entry of the infection.

Prodromata V S continued to work in the laboratory during the following week. On April 8, nine days after the conjunctival inoculation, she noted the onset of fatigue and chilliness, although her temperature was not taken. On the following day chilly sensations and asthenia persisted, and her temperature was found to be 103°F. She had no headache. On April 12 she was admitted to the hospital with the clinical picture of "la grippe," consisting of fever, chilliness, increasing weakness, fatigue and insomnia. In spite of these symptoms, she showed moderate euphoria. During the next four days there was a remission of fever, but asthenia persisted.

Meningitis On April 17, nineteen days after the conjunctival inoculation, she developed a persistent headache with fever and a stiff neck. Two days later she became nauseated

and vomited several times. The vomiting ceased on the following day but the headache and stiff neck remained for one week after their onset. At the height of the meningeal symptoms the temperature rose to 102°F and then fell to normal. A neurological examination performed during the meningeal phase of the illness revealed a positive Kernig's sign and exaggerated reflexes. In the course of her illness she lost 20 pounds.

Course. During the next two weeks there was a daily rise of temperature of 0.5° to 1.0°F after which the temperature remained normal, and the patient got out of bed on May 3. Illness persisted for several months then disappeared. Seven weeks after meningitis the patient had regained 20 pounds and she recovered completely from all residual neurological signs or symptoms.

Isolation of the virus. The virus of lymphocytic choriomeningitis was isolated from the patient's blood on April 26. Toxinular puncture was none "for the diagnosis was obvious and traumatic was to be avoided."

Observations on complement-fixing antibody. Blood sera drawn from the patient on April 26 and 29 showed an increase in the titer of complement fixation "from 10 to 15 units."

Comments. The portal of entry of the virus in this case was probably through the conjunctival mucosa. The prodromal illness with remission of fever before the onset of meningitis was similar to that observed in the experimental infections. The incubation period from the time of accidental inoculation to the onset of meningitis was nineteen days. Following the meningeal phase of the illness convalescence was prolonged with slight fever and early fatigue but followed by complete recovery.

The clinical and experimental observations which have been described present details of the clinical picture of the meningeal form of infection.

2 Encephalomyelitic form. In 1935 Findlay, Alcock and Stern (27) in England described the first two cases of the encephalomyelitic form of lymphocytic choriomeningitis. In these cases the signs and symptoms were consistent with infections of the brain substance as well as of the meninges. The clinical histories of these two patients will be presented.

Case 1. A 24-year-old man developed a headache with pain in his back and a fever of 102°F on September 12, 1935. During the following nineteen days he ran an intermittent fever which rose nightly to 101°F and then returned to normal.

On October 5 twenty-three days after the onset of the febrile prodromal illness, he became confused and developed hallucinations. On the following day his lower abdomen and legs became tender and painful. On October 11 he noted some difficulty in lifting his left leg and on the following day both legs became completely paralyzed. On October 17 he was still mentally confused, he could not give a connected history and he occasionally used wrong words. With the exception of early bilateral papilledema, the cranial nerves were normal. The movements of the arms were normal. However he was not able to sit up and the only movements possible in his legs were contractions of the right quadriceps and weak movements of the right ankle and toes. From the umbilicus to the level of the fourth lumbar segment there was marked paresthesia and below this level all forms of sensation were impaired. The calf muscles were tender on pressure. There was complete retention of urine. The maximum cerebrospinal fluid cell count was 336 cells per cu mm with 57 per cent lymphocytes.

Motor power gradually returned to his legs. One month later he could lift his right ankle from the bed although the left leg was still paralyzed. He began to pass urine naturally on November 22 and by November 26 somatic sensation had returned to normal. During the next few months progress continued so that he was able to walk.

Spinal fluid removed from the patient on October 15 was inoculated into mice and into a monkey. A strain of the virus of lymphocytic choriomeningitis was recovered and it was

shown that this strain was serologically identical with the American strain of the virus. Serum drawn from the patient after recovery contained neutralizing antibodies.

Case 2 B C, a 36-year-old man, developed a slight head cold with sneezing and malaise about October 17, 1935. Two days later his voice almost disappeared, and he had two or three chills. The following day he felt better, and he remained well for four days. On October 24 he felt ill again and complained of an aching pain in his back and of insomnia. The back pain spread from the lumbar region to the dorsal area, became more severe for a few days, and then diminished in intensity.

On October 31 (fourteen days after the onset of prodromal symptoms), he noticed tingling in his fingertips and weakness in his grip. He also found that his sense of taste was impaired, and that his teeth "felt too big." In addition, he had slight difficulty in urination. On the following day numbness and tingling in his feet developed. His legs became progressively weaker until he was unable to walk without support. Partial right facial paralysis developed, and transient diplopia occurred. He had urinary retention. His temperature was 100°F. On physical examination there was a right facial palsy of lower-motor-neurone type, and a slight ptosis of the left eyelid. Otherwise the cranial nerves were normal. The movements of both arms, especially at the shoulders, were quite weak. He was unable to sit up in bed. The movements of both legs were so weak that he was unable to stand. All tendon jerks were absent. The upper abdominal reflexes were normal, but the lower abdominals were diminished. The plantar responses were both extensor. There was a loss of all sensation in the arms and also some impairment in the legs. On November 11 he developed complete right facial paralysis. Cerebrospinal fluid drawn on November 6 revealed 63 cells per cu mm.

Motor power gradually returned, so that by November 29 he was able to walk and to use his arms normally. Complete right facial palsy persisted. Sensation returned by this time but the tendon jerks were still absent, and the plantar responses remained extensor.

The virus was isolated by the injection of the patient's spinal fluid into mice. Serum drawn from the patient after recovery contained neutralizing antibodies.

These two proved cases of the encephalomyelitic form of lymphocytic choriomeningitis are the best examples of this clinical picture which have been described. After a prodromal febrile illness, evidence of damage to the brain and the spinal cord appears. Convalescence is prolonged, but there is considerable restoration of function in the damaged nerve tissue.

Howard (34) has described three cases of this type of infection in New Haven, Conn. In each patient a prodromal illness was followed by encephalitic symptoms. The virus was isolated from the spinal fluid of one case, who died five months later in a mental hospital. In the other two patients, the encephalitis was fatal in 7 and 9 days, and the virus could be isolated only from brain tissue which had been kept in glycerine. This work must await confirmation, since the virus studies were somewhat atypical.

8 Non-meningeal form (a) *Evidence for its existence* The first proved case of systemic infection with the virus of lymphocytic choriomeningitis was described in 1941, although the existence of such cases had been suspected since 1935. Considerable evidence had been amassed to show that individuals developed immunity to this virus without a history of any central nervous system disease. In some cases a "grippal" illness preceded this immunity, while in other cases the immunity was apparently not associated with any illness. The evi-

dence in support of non-meningeal infections with this virus will be presented in chronological order

Immunological studies of human blood sera In 1935 Armstrong and Wooley (21) reported the case of L O P This 38-year-old, colored, married man was an attendant at the National Institute of Health, where he "occasionally handled infected monkeys" One year previously he had been absent for four days with "grippe," but there was no history suggestive of any central nervous system involvement Since his serum showed a high titer of protective antibodies, it seemed probable that his immunity to the virus was the result of a "systemic infection without involvement of the central nervous system"

An epidemic of lymphocytic choriomeningitis in mice developed in 1935 at the Rockefeller Institute, Princeton, N J (35) In February, 1935, Traub found that three guinea pigs in his laboratory had also become infected with the virus In studying the spread of this virus, he examined successive sera from J S, the caretaker of these infected guinea pigs On March 5, 1935, his serum showed no protection, on July 20, 1935, it showed moderate protection, and on September 16, 1935, it showed strong protection The caretaker had developed immunity to the virus during this period of five months, although he had had no illness suggestive of meningitis This serological evidence is adequate to show an inapparent infection with this virus Traub also studied the serum of J M, who had taken care of the infected mouse colony for five years His serum likewise showed strong protection against the virus

From 1935 to 1940 Armstrong and his co-workers (16, 21, 36, 37, 38, 39) studied 2000 human sera from all parts of the United States for the presence of antibodies against the virus of lymphocytic choriomeningitis Of 1000 sera from persons who gave no history of any central nervous system disease, 10 per cent possessed moderate or strong neutralizing antibodies The results of these serological studies have been confirmed by Yamarat (40) He tested the sera of 126 patients who were in the hospital for a variety of illnesses, chiefly pneumonia and heart disease Most of these individuals had their homes in or near Boston, Mass In this group, 14 sera showed moderate protection, and 1 serum showed strong protection against the virus Thus 11.8 per cent of the sera showed the presence of antiviral None of these individuals had any history of central nervous system disease at any time The results of these protection tests, which are a specific measure of antibody titer against this virus, strongly suggest that part of the population is exposed to this agent and develops immunity to it, without any evidence of meningitis

Serological studies were made on the sera of 106 individuals with a history of a recent upper respiratory infection, designated as "grippe," influenza, or a "cold" without meningeal irritation (36) Of this group, 28 per cent showed moderate or strong protective antibodies against the virus This percentage is significantly greater than the 10 per cent of positive sera among 1000 chosen at random Although this statistical evidence is not conclusive, it supports the view that a "grippal" infection with the virus does exist

(b) *Experimental infections* In 1937 Kreis (13) first described experimental

human cases of the purely systemic form of lymphocytic choriomeningitis virus infection. These individuals constituted half the total group of patients who had received subcutaneous inoculations of this virus. In these cases fever developed after an incubation period of $1\frac{1}{2}$ to 2 days, followed by grippe-like symptoms. However, these prodromata were not followed by a meningeal reaction, but by complete recovery. Kreis (13) made a detailed report of one of these cases. The clinical findings in this patient are presented in Figure 4.

Case history D. M. received a subcutaneous inoculation of 2 cc. of an emulsion of infected mouse brain. On the following day he felt feverish and his temperature was 101.5°F . The initial wave of fever lasted eight days and was accompanied by chilliness, malaise, and

DM. EXPERIMENTAL VIRUS INFECTION WITHOUT MENINGITIS

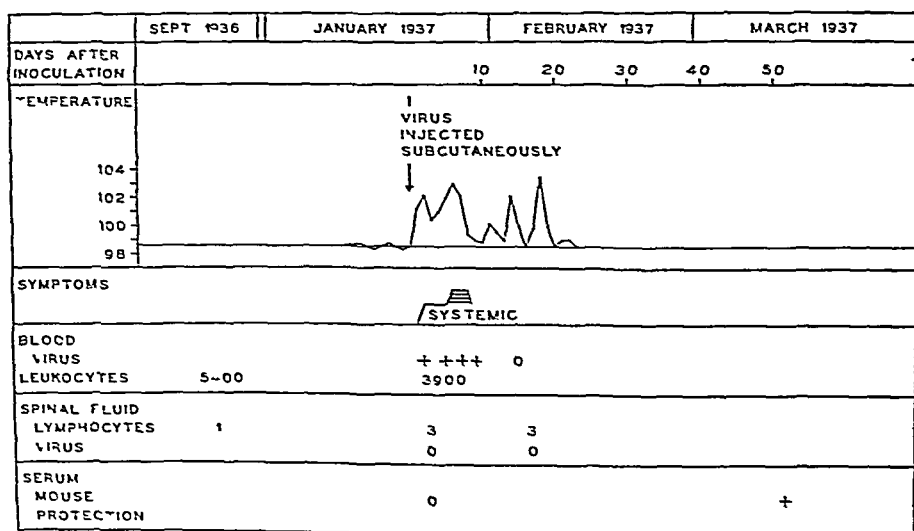


FIG. 4. COURSE AND ESSENTIAL LABORATORY DATA IN A CASE OF EXPERIMENTAL LYMPHOCYTIC CHORIOMENINGITIS, NON-MENINGEAL FORM.

Patient was inoculated subcutaneously with 2 cc. of an emulsion of infected mouse brain. (After Kreis (13).)

prostration at the height of the fever. A white blood cell count revealed a leukopenia of 3900 cells per cu. mm. on the fifth day of illness. All symptoms disappeared with the remission of fever. This febrile wave of infection was followed by three asymptomatic waves of fever of two to five days' duration. The undulating febrile reaction covered a span of 22 days, during which time no meningeal symptoms developed. He had no headache at any time. Lumbar punctures performed on the third and seventeenth days after inoculation showed no cellular reaction or chemical abnormalities in the spinal fluid.

Four samples of blood taken from the second to the ninth day after inoculation all contained virus. However, a sample of blood taken on the fifteenth day of the disease showed no virus. No virus was isolated from the specimens of spinal fluid removed on the third and seventeenth days of his illness. As a result of this systemic infection, he developed antiviral in his blood.

This experimental evidence suggests that the virus can produce a systemic infection with fever, malaise, and prostration, but not followed by meningitis. Such an infection has an incubation period of $1\frac{1}{2}$ to 3 days before the onset of the febrile reaction, and of 6 days before the development of prostration. Fever without other symptoms may recur over a three-week period. From the second to the tenth day after inoculation, the blood contains virus. A leukopenia occurs during the febrile period.

(c) *Spontaneous laboratory infection* The first proved case of spontaneous infection without meningitis was described by Armstrong and Hornibrook in 1941 (16, 41). The clinical chart of the patient is shown in Figure 5.

V. H., a 31-year-old white male, was engaged in research study of the virus of lymphocytic choriomeningitis. In the months preceding his illness, he handled chiefly white mice,

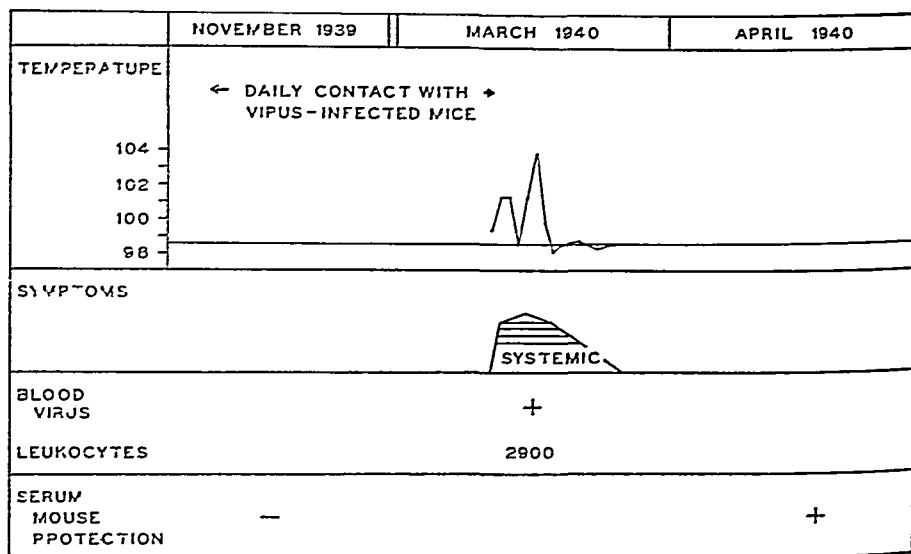


FIG. 5. COURSE AND ESSENTIAL LABORATORY DATA IN A CASE OF SPONTANEOUS LABORATORY INFECTION, NON-MENINGEAL FORM
(From Armstrong and Hornibrook (41))

which were carrying the congenital type of infection. No circumstances in his history throw any light on the possible incubation period of his illness (42).

On March 11, 1940, he noticed troublesome pains in his arms, shoulders, and back. His temperature was 99.4°F. On the following day he felt ill, lost his appetite, and complained of increased lumbar back pain. The back pain became more severe and required codeine for relief. Physical examination was negative with the exception of a flushed face. The temperature rose to 101.3°F, fell to normal for a day, then rose again in a second wave of fever, which lasted four days, and returned to normal. A white blood cell count on March 15 revealed a leukopenia of 2900 cells. The chief symptoms were backache, marked prostration, and weakness.

Although the acute illness lasted only one week, weakness and prostration persisted during the following week. However, the evening temperature did not rise above normal during this second week. No headache, vomiting, stiff neck, or photophobia developed after this systemic infection. Neurological examinations during the course of his illness were completely negative.

The virus of lymphocytic choriomeningitis was isolated from his blood on March 15, the fifth day of fever. Blood drawn from the patient four months before this illness (November 22, 1939) showed no protective antibodies. However, serum drawn six weeks after the illness (April 28, 1940) showed strong protection.

Case summary This influenza-like, clinical picture was characterized by fever of 100 to 104°F of one week's duration. It was accompanied by prostration, pain in the lumbar back, the arms, and the shoulders, weakness, and anorexia. The virus of lymphocytic choriomeningitis was isolated from the patient's blood during the illness, and antiviral developed in his serum after a short convalescence. This is the only proved spontaneous case of systemic infection with the virus of lymphocytic choriomeningitis. In addition, another probable case will be briefly described because of the unusual clinical picture associated with it.

A probable case of non-meningeal infection Yamarat (40) developed a brief illness during the course of research work with the virus of lymphocytic choriomeningitis. He was engaged chiefly in the isolation of the virus from grey mice, although he also handled experimentally infected white mice.

On February 25, 1940, he had an attack of follicular tonsillitis, which lasted four days with a temperature of 100°F. He complained of severe, dull,

TABLE 3

The clinical forms of infection with the virus of lymphocytic choriomeningitis

MENTINGEAL FORM	ENCEPHALOMYELITIC FORM	NON-MENTINGEAL FORM
1 Systemic illness	1 Systemic illness	1 Systemic illness
2 Meningitis	2 Encephalomyelitis	
3 Convalescence	3 Convalescence	2 Convalescence

frontal headache for one day. From this illness he rapidly recovered with no signs of meningeal infection.

No attempt to recover a virus from his blood was made. On November 15, 1939, three months before this illness, his serum showed no protective antibodies. One month after the illness, March 23, 1940, his serum did show slight protection.

This clinical picture of fever, headache, and tonsillitis is quite different from symptomatology in the proved case of non-meningeal infection. The variability in symptoms produced by a systemic infection with this virus will not be known until a series of proved cases has been observed.

4 *An outline of the clinical picture* The three clinical forms of infection fit into a single pattern (Table 3). In all types of this disease, the virus first invades the blood stream and produces a prodromal or systemic illness. After this, in the meningeal and encephalomyelitic forms of infection, the virus invades the central nervous system. In the non-meningeal infection this second phase does not occur. In all forms there may be a period of slow convalescence.

In the following outline, the systemic illness produced by the virus in all three types of infection will be summarized as a single picture. Then the central nervous system effects of virus invasion will be described. In each form of infection the nature of the convalescence will be reviewed.

(a) *Prodromal or systemic infection* (1) *Incubation period* From $1\frac{1}{2}$ to 3 days after experimental inoculation of the virus into human beings a fever develops and the virus is present in the blood. The prodromal symptoms develop five to ten days after exposure to the virus, and they are of 7 to 20 days' duration.

(2) *Symptoms* *Fever*, ranging from 100 to 103°F, usually occurs in two or three waves, one of which may last a week. Chilly sensations and unusual warmth may be noted. Between the undulations of the fever the temperature may be normal for several days. Usually a remission of fever occurs before the onset of meningitis or encephalomyelitis. *Grippe*, characterized by malaise, generalized pains, lumbar backache, and muscle aches, frequently forces the patient to go to bed. With remission of fever, he feels well and gets up. *Physical fatigue, weakness, and lethargy* are often noted. An *upper respiratory infection* occasionally occurs from one to two weeks before the onset of meningitis. The patient may complain of a cold, cough, sore throat, tonsillitis, or bronchitis. *Mild headache and light-headedness* may be noted. A relative *euphoria* sometimes accompanies this systemic illness. Considerable *loss of weight* may occur.

(3) *Physical signs* Fever, a flushed face, and occasionally an inflamed throat, are the only positive physical findings.

(4) *Laboratory findings* During the prodromal illness, the virus is present in the blood. There is a definite leukopenia, with granulopenia and relative lymphocytosis and monocytosis at first. After a few days an eosinophilia of 5 to 8 per cent may appear (43).

(b) *Central nervous system infection* *Meningitis* (1) *Incubation period* After a period of 15 to 23 days, there is an acute onset of fever, headache, and vomiting. This meningeal reaction, which lasts from 7 to 30 days, gradually recedes and is followed by recovery.

(2) *Symptoms* *Fever* usually varies from 101 to 104°F and is accompanied by chilliness without shaking chills. After 1 to 3 weeks the temperature falls to normal by lysis. *Headache* is usually generalized and bilateral. *Nausea and vomiting* are associated with a loss of appetite. These three symptoms of meningeal irritation are present in nearly all cases (Table 4). *Lumbar backache* occurs frequently. *Drowsiness, disorientation, or memory defects* for recent events may be noted occasionally. *Physical weakness and fainting* may accompany an inadequate food intake with fever. *Abdominal and thoracic pain* have been reported. *Constipation* may appear before the onset of meningitis and persist for several days.

(3) *Physical signs* The temperature may be markedly elevated with a normal or only slightly accelerated pulse. The tissues are often *dehydrated*, and there may have been a *weight loss* of 10 to 20 pounds in the preceding three-week period. *Photophobia* is often marked, and it usually persists longer than the meningeal signs. *Slight papilledema* occasionally occurs in association with increased intracranial pressure. *Stiff neck* is nearly always present, although the patient often does not complain of it. *Nuchal rigidity* only lasts a few days. *Kernig's sign* is positive in more than half the cases (Table 4). *Brudzinski's neck and leg signs* and *Guillain's sign* are less frequently demonstrable. Lo-

calized *reflex changes* (hyperactivity or hypoactivity) occur in one-half of the individuals. The knee jerks may disappear for a week and then return to normal. In one case an absent triceps jerk was the only reflex change. A transient Babinski sign occurs in one-third of the cases. Slight muscle weakness and occasional abdominal muscle spasm may occur. There are probably no skin manifestations in this disease. However the presence of dry scaly skin on the extremities in two cases may be related to this virus infection.

(2) *Laboratory findings* a) Blood. A normal *white blood cell count* and a normal *differential count* are most frequently found. Although the leukocyte count usually varies between 6 000 and 11 000 cells it occasionally is as high as 20 000 cells per cu mm. with the increase mainly in the polymorphonuclear leukocytes. No anemia develops in this infection. On the contrary there is often an increase in the *red blood cell count* of 1 to 2 million cells per cu mm. The *sedimentation rate* is normal or slower than normal. In one case it did not

TABLE 4

The frequency of signs and symptoms in the meningeal phase of 25 cases of lymphocytic choriomeningitis

(Modified from Baird and Rivers (31))

	PRESENT	ABSENT	NO RECORD
<i>Symptoms</i>			
1 Fever	20	2	1
2 Headache	20	2	1
3 Nausea and/or vomiting	18	5	0
<i>Physical signs</i>			
1 Nuchal rigidity	18	1	4
2 Kernig's sign	12	5	6
3 Hyperactive reflexes	4	14	5
4 Hypoactive reflexes	6	12	5
5 Babinski's reflex	7	9	7

rise above 4 mm per hour throughout the meningeal phase of the illness while in a second case it was 10 mm per hour. The virus can occasionally be isolated from the blood during the first few days of meningitis but after that it is no longer detectable. At this phase of the infection no complement fixing or neutralizing antibodies are present in the blood.

b) *Cerebrospinal fluid*. The fluid is usually clear or slightly turbid and it rarely shows a fibrin clot on standing. It is under normal or increased pressure. The maximum *cell count* in the fluid varies in proved cases from 63 to 3 200 cells per cu mm. of which 95 to 100 per cent are usually lymphocytes. In a few cases only 80 per cent of the cells may be lymphocytes. A small percentage of large mononuclear cells and polymorphonuclear leukocytes may be present. However, the reaction is predominantly lymphocytic in the spinal fluid. In one half of the cases the cell counts rose above 1200 cells per cu mm. during the early meningeal phase.

The *sugar content* is usually normal, although it may be reduced to 35 to 40 mgs per cent. This reduction is associated with a low normal blood sugar in a fasting person. The *chloride content* is usually normal, but it too may be reduced as a result of vomiting and depletion of serum chlorides. The *protein content* is usually slightly elevated to 50 to 200 mgs per cent, although it may remain normal. The *colloidal gold reaction* is usually normal, but any form of curve may occur. A change in the meningitic zone is most common.

The *virus* can be isolated from the fluid during the first 7 to 10 days of meningitis, but after that time it is no longer detectable. Stained smears show no organisms, and cultures of the fluid are negative.

c) *Urine* Normal

(c) *Central nervous system infection* *Encephalomyelitis* (1) *Incubation period* After a prodromal illness of two to three weeks, an encephalomyelitis may develop.

(2) *Symptoms* Along with fever and headache, *mental confusion* and *hallucinations* appear. The patient is *drowsy*, and there may be *aphasia* or *diplopia*. Complaints of tender, painful, and weak muscles may be followed by complete *paralysis* in the legs. *Tingling* and *numbness* of the extremities occur. There may be *transient urinary retention*.

(3) *Physical signs* The patient's memory for recent events is fragmentary and he may be disoriented. Slight *bilateral papilledema* of the optic discs may be present. Due to *muscle weakness*, he may be unable to sit up, to raise his legs, or to walk. In one case *facial paralysis* was complete and permanent. *Loss of sensation* may develop in the extremities. All *tendon reflexes* disappear, and *Babinski's sign* may be present.

(4) *Laboratory findings* The spinal fluid and blood studies reveal the same picture as that found in the meningeal form of infection.

(d) *Convalescence* (1) *Systemic form* Since the virus does not invade the central nervous system, the patient recovers completely after 1 to 2 weeks of physical fatigue and malaise.

(2) *Meningeal form* After the meningeal irritation has subsided, the patient's health returns to normal in 15 to 60 days. Slight *fever* usually continues for 1 to 2 weeks with an evening rise to 99.5° to 100°F. The *weakness* and *fatigue* accompanying the meningitis slowly disappear in a few weeks. The appetite returns and there is a slow *weight gain*. The *altered reflexes* return to normal during early convalescence. The *cellular reaction* in the cerebrospinal fluid usually decreases to 10 to 15 cells per cu mm within 4 to 6 weeks after the onset of meningitis, although a moderate cellular reaction has persisted in a few cases for 4 to 6 months. Although recovery is usually complete, personality changes, prolonged fatigue, headache, impairment of memory, mental depression, dizziness, and strabismus are occasional sequelae (27, 28, 44, 45). In one case there were five attacks of meningitis over a five-month period, finally followed by recovery (26). In another instance, chronic arachnoiditis developed as a complication of lymphocytic choriomeningitis (24). This patient developed a spastic paraplegia, which was not relieved by surgical intervention. Of the

proved cases of this infection none have been fatal, although fatal cases of acute aseptic meningitis have been described, several of which probably were due to choriomeningitis virus

(8) *Encephalomyelitic form* Recovery from encephalomyelitis is prolonged and may not be complete. In the reported cases somatic sensation and bladder function returned to normal. However, one patient had a permanent paralysis of her legs, and another one had a persistent right facial palsy. Alterations in reflexes may be permanent.

In all forms of infection with this virus, complement fixing and neutralizing antibodies develop in the patient's serum after recovery.

E Lymphocytic choriomeningitis virus

1 *Historical* The virus of lymphocytic choriomeningitis was discovered in 1934 by Armstrong and Lillie (11) in the course of studies on St. Louis encephalitis virus. Material from one patient, after 5 serial passages through monkeys all of which developed the typical picture produced by the St. Louis virus, was inoculated intracerebrally into a sixth monkey immune to the latter agent. In this animal a disease characterized by fever, tremors, sluggishness, and a lymphocytic meningitis, appeared on the fifth day after inoculation. This disease was transmitted to other monkeys, mice, and guinea pigs, and was shown to be due to a filterable virus, which was named the virus of lymphocytic choriomeningitis, because of the pathologic picture it produced. The authors suggested that this virus might play a rôle in human disease since it was so readily transmissible to other animals, and noted that the monkey disease closely resembled Wallgren's "acute aseptic meningitis". The following year, Armstrong and Wooley (21) reported the isolation of this same virus from the brain of a patient with a peculiar encephalitis, and from the brain of a monkey inoculated with a monkey strain of poliomyelitis virus. They studied 166 human sera for protective antibodies and noted that three gave strong protection. One of these was from a patient who had had an encephalitis in 1934, another from a laboratory attendant who occasionally handled infected monkeys and who had had "grippe" in 1934, and the third from a patient who had recovered from typical "acute aseptic meningitis".

In 1935, Traub (17) described a spontaneous disease which was endemic in a colony of laboratory white mice. He found that 50 per cent of the colony was infected, but symptoms appeared in less than 20 per cent, while only 2 per cent died. Symptomatic infection occurred only in mice 2 to 6 weeks old, but the presence of virus in older mice that seemed perfectly well could be demonstrated by the intracerebral injection of sterile broth. This was followed by the development of a disease characterized by convulsions, spasticity, and death, which was serially transmissible by intracerebral injection to normal mice or guinea pigs.

Shortly thereafter, Rivers and Scott (18) reported the isolation of a virus from two patients with "acute aseptic meningitis" and proved its etiological rôle in their disease. An admirable description of the procedures used will be found

in the papers of Scott and Rivers (23), Rivers and Scott (46), and Rivers (15). The three groups of workers who had discovered these viruses exchanged material, and it was shown conclusively by cross neutralization tests that Armstrong's monkey virus, Traub's mouse virus, and Rivers' and Scott's human virus were identical (46, 47, 48).

Subsequently, isolation of this virus has been reported from human cases of aseptic meningitis and from animals in various parts of the world and serologic proof of its etiologic rôle in a number of cases of human disease has been established.

2 Nature of the virus (a) Size In size lymphocytic choriomeningitis belongs with the smaller, but not the smallest viruses. It will pass through Berkfeld V, N and W filters (46) and a Chamberland L₃ candle (49). Although Scott and Rivers (46) reported that it was partially retained by a Seitz filter, Casals-Ariet and Webster (50) used repeated Seitz filtration to separate it from rabies virus. The latter was held back, while the virus of choriomeningitis appeared in the filtrate.

The results of all attempts to measure the size of a virus by ultrafiltration depend upon the virulence of the virus and the delicacy of the method for detecting its presence in the filtrate. Thus Rivers and Scott (46) originally obtained a size of 150 to 100 millimicrons for choriomeningitis virus by filtration through graded collodion membranes. The filtrate was tested to see whether it would produce symptoms of the disease in mice. Scott and Elford (51) devised the more delicate technique of testing all inoculated mice for immunity. They obtained the revised figure of 40 to 60 millimicrons, which compares favorably with their figure of 35 to 55 millimicrons obtained by ultracentrifugation. Casals-Ariet and Webster (50) isolated an exceedingly virulent strain of the virus from their rabies tissue cultures and obtained a size of 33 to 50 millimicrons by ultrafiltration. Smadel, Baird, and Wall (52) were able to concentrate the virus by high speed centrifugation at speeds of 20,000 to 30,000 r p m for 30 minutes, but not at speeds of 3500 to 5000 r p m.

(b) Preservation and stability Most workers have found that infected tissues retain their virulence for long periods when preserved in neutral buffered glycerine at 5°C, when frozen rapidly and kept at -40°C (46, 49, 53), or when desiccated from the frozen state. Smadel and his co-workers (52) found that the virus deteriorated rapidly in salt solution or various buffer mixtures, but that it was stable enough to survive such procedures as filtration and ultracentrifugation when it was suspended in physiological saline containing 2 per cent inactivated normal guinea pig serum. Lépine's strain isolated from Parisian white mice was likewise unstable at room temperature and would not survive desiccation unless it was first frozen (49). In our work, we have found considerable differences between strains. A standard laboratory strain lost its virulence in an hour or two at room temperature, whereas two freshly isolated strains, one from a patient and another from wild mice, were much more stable.

(c) Cultivation of the virus Bengston and Wooley (54) were the first to cultivate the virus of choriomeningitis. Using one of Armstrong's strains, they

carried the virus through 8 passages by inoculating the chorio-allantoic membranes of 11-day chick embryos. The virus present in the ground brain and membrane of the embryo could be filtered through a Berkfeld N candle and concentrated by centrifugation at 15,000 r.p.m. before passage. Virus was found in the membrane, liver, brain, and amniotic fluid. The embryos took longer to die than mice, and as with many other viruses, the newly hatched chick was found to be immune.

MacCallum and Findlay (55) made a very thorough study of the properties of this virus in tissue culture, carrying 3 strains for 270, 38, and 35 subcultures at 4-day intervals. The Maitland method was used with a medium of 1 part of normal human serum and 9 parts of Tyrode's solution in which minced chick-embryo tissue was cultivated. Their most interesting finding was a change in the virus which occurred at about the 66th passage. It then produced a disease of several days' duration in mice characterized by flaccid paralysis instead of the usual brief illness terminating in spasticity and convulsions. At the same time, the virus lost virulence for guinea pigs, but its original properties could be restored on intracerebral passage through guinea pigs.

The virus of choriomeningitis has been inadvertently cultivated in tissue cultures at least once. Casals-Ariet and Webster (50) encountered it as a contaminant in their rabies virus tissue cultures. They felt that it came from the monkey serum rather than the mouse brains, since there was an epidemic of choriomeningitis infection among the stock monkeys at that time. Laigret and Durand (56) reported the finding of a virus with many similarities to choriomeningitis virus in the mouse strain they used for making mouse brain yellow fever vaccine. They isolated the same virus from the spinal fluid of a man who developed benign lymphocytic meningitis following yellow fever immunization.

(d) *Pathogenicity* (1) *Mice* (i) *Natural infection*. As indicated above, choriomeningitis virus is a naturally-occurring parasitic agent in mice. It has been isolated from strains of laboratory white mice in the United States (17), England (27), France (29), and Japan (30), and from grey mice (*mus musculus*) in the United States (40, 57, 58, 59).

The spontaneous disease produces a very different clinical picture from the artificial one resulting from intracerebral injection of the virus. Traub has made a very careful study of this infection in a colony of white mice, since he first isolated the virus from them in 1935 (17). When the disease was first observed (48), he noted that about 50 per cent of the mice in the colony were infected, but that only about 20 per cent of these showed symptoms of infection. These were emaciation, somnolence, and slow growth, and were observed only among the mice of from 2 to 6 weeks of age. Mortality among infected mice was less than 2 per cent, and almost all of them recovered completely. He used two methods to detect infection: direct isolation of the virus by the intracerebral injection of suspected material into guinea pigs or normal mice, or its indirect demonstration by the intracerebral injection of sterile bouillon. Following the latter procedure, as infected mouse would develop convulsions in 3 to 13 days and the virus could be isolated from the brain at death. Traub

found that the virus was present in the blood, brain, urine, and nasal secretions of the naturally infected mice, even though they showed no symptoms whatsoever.

In subsequent studies, Traub (60, 61) noted two types of immunity in mice that had been naturally infected: "infection immunity," in which virus persisted in the body for long periods of time, and "sterile immunity," in which the mouse was resistant to infection, but neither virus nor neutralizing antibodies were present in the peripheral blood. He found that virus seemed to persist longest in the mice if they were naturally infected *in utero* or by contact soon after birth if the disease were severe, as in experimentally infected older mice or if a particularly virulent strain of virus were used (62). By segregating a group of infected mice for study in separate cages, Traub (35) was able to follow the natural course of the infection in a closed unit. Under these artificial conditions 100 per cent of the mice became infected and virus persisted in the blood, urine, and nasal washings for at least 4 to 5 months. He found that mice were frequently infected *in utero*, and the young mice then showed a high incidence of symptoms with a mortality rate varying from 0 to 60 per cent. If older mice were added to the colony and infected by contact, they developed no symptoms, but became immune. By the use of screened cages he came to the conclusion that contact infection probably occurred by way of the nasal secretions rather than the urine. In an attempt to find the source of infection for their laboratory mice Traub trapped a large number of wild mice about the buildings but was unable to demonstrate evidences of infection in a significant number of them. In a recent paper Traub has summarized the changes that have taken place in this disease in his mouse stock during four years (63). The infection originally produced symptoms in many and death in some mice infected *in utero* (many were infected by contact after birth). Now 100 per cent of the mice acquire the infection *in utero* and remain carriers throughout life, with virus in their organs and blood. At present the virus produces symptoms only in suckling mice from a virus-free stock, and experimentally-infected mice never transmit the infection to others.

Hias (64) has made a similar study in white mice, and his findings confirm those of Traub. He noted that mice infected *in utero* or in early infancy tended to transmit the infection to their offspring and contacts. Mice infected after reaching maturity retained only active virus for a short period and such females did not transmit the disease to their young except when pregnant at the time of inoculation. Contact infection occurred when exposure through sexual contact, urine and feces was eliminated, thus emphasizing the importance of saliva and nasal secretions in the transmission of the natural disease in mice. Instillation of semen from infected males into the vaginas of normal females produced infection in a number of mice but these females have later produced litters of uninfected mice. Hias recovered virus from pooled feces of infected mice but when fresh mice were placed in an uncleaned cage inhabited for 22 days by infected mice, and in which contact infection had occurred, none of them contracted the disease. Seven naturally infected house mice trapped in Washington

homes showed no symptoms while observed for 5 months, but were able to transmit infection to normal white mice placed in the cage with them. These mice likewise showed no symptoms. The authors (59) were able to demonstrate the *in utero* transmission of the natural infection in house mice by isolating virus from the pooled organs of a pregnant female grey mouse and also from the fetuses removed from her in such a way as to avoid contamination with her blood.

Thus, there seems no doubt that the natural infection in mice is usually acquired *in utero* or in very early life and that it passes from generation to generation as an asymptomatic congenital infection. Many of these mice are carriers of active virus and excrete it in their urine, feces, semen and nasal secretions.

(1) *Experimental infection* When uninfected mice are injected with virus there is a marked difference in the results depending upon the route of inoculation (11 15 46 48). With subcutaneous injection most mice develop immunity in a few days (65) without any symptoms but an occasional mouse may appear ill for a few days and recover. On intraperitoneal injection the results are similar, but with highly virulent strains of virus and particularly with strains isolated from naturally infected mice a fatal illness may be produced.

Intracerebral injection however produces a characteristic and fatal disease with great regularity, once a virus strain has had several intracerebral passages in mice. The incubation period is 5 to 6 days and the illness itself rarely lasts more than 1 to 2 days unless the mice recover. On the sixth or seventh day the mice begin to lie parallel to one another huddled at one side of the cage with their hair ruffled and eyes half closed. If carefully observed for the next 24 hours they may be seen to develop seizures characterized by clonic convulsions of the whole trunk and finally a spastic extension of the hind legs. The latter point is characteristic of the disease and mice found dead in the cages show marked *rigor mortis* with the hind legs in full extension and spread apart. Mice often die with their first seizure but some may have several before death. Seizures can be induced in sick mice by twirling them by the tail. When the convulsion starts the tail vibrates like a taut musical string with occasional violent jerks and after a few moments the hind legs slowly go into their characteristic extended position. Such a mouse when returned to the cage either dies very quickly or lies on his side gasping for a few moments and then begins to drag himself around with his spastic hind legs and tail extended. Death usually occurs from the 7th to the 10th day after inoculation. Most mice that survive the tenth day recover, though they may appear dirty ill-kempt listless and emaciated for a week more. After a while they begin to eat and about three weeks after inoculation look like normal mice again. Intracerebrally injected mice who have symptoms but recover are immune to subsequent intracerebral inoculations. In our experience those that do not show symptoms have no significant immunity but this is somewhat at variance with the general experience.

(2) *Guinea pigs* In guinea pigs lymphocytic choriomeningitis virus produces a rather different but quite characteristic clinical picture (11 15 46 48). Spon-

taneous infection of guinea pigs may occur and can cause a considerable mortality. Shaugnessy and Zichis (66) have shown that not only can the virus penetrate the lightly scarified skin of these animals, but it may also produce infection when dropped on the unbroken skin. The experimental disease is essentially the same, regardless of the route of injection, whether subcutaneous, intraperitoneal, or intracerebral, although the incubation period and course are shorter by the latter route. After an incubation period of 2 to 4 days, the animal develops a fever (104° to 106°F), loses its appetite, and begins to look dirty, ruffled, and sick. Conjunctivitis and diarrhea may occur after a few days. The most striking change is the progressive emaciation which becomes very noticeable shortly before death. Many of the animals develop labored breathing and become so weak that when placed on their side they are unable to right themselves. Depending upon the virulence of the strain, death occurs from about the 8th to the 16th day. After the period of fever, the temperature falls quite characteristically to subnormal levels for a day or two before death. The picture of emaciation, weakness, and diarrhea in the latter stage of the disease is one that may be quite difficult to differentiate from scurvy. Virus may be isolated in large amounts from the blood, spleen, adrenals, and lungs of the animals dying of the disease (67). Guinea pigs do not become carriers of the virus after infection.

(3) *Monkeys* In the monkey, spontaneous lymphocytic choriomeningitis is a disease quite similar in many ways to the human disease. Inapparent and relatively asymptomatic infections may occur, as evidenced by the number of monkeys found to have neutralizing antibodies (21, 37, 50). On the other hand, symptomatic infection also occurs, and Coggeshall (68) has recently reported a very severe epidemic due to this virus in a group of monkeys in his malaria laboratory. This infection involved the respiratory tract and serous cavities predominantly, and the monkeys had bloody nasal discharge. The possibility of mosquito transmission was raised, since he showed that *Aedes aegypti* could transmit the disease from infected to normal guinea pigs.

Monkeys can be infected by light scarification of the skin, by instillation into the urethra or vagina (37, 69), and by subcutaneous, intraperitoneal, or intracerebral inoculation (11, 37, 46, 69). The latter method produces the most regular results. The animals develop fever 5 to 14 days after inoculation. This lasts a few days and is followed by anorexia, sluggishness, and mild tremors or hyperesthesia. At this later stage a lymphocytosis as high as 1500 cells per cu mm may be found in the spinal fluid. Armstrong and his associates (70) have shown that the virus is widely distributed throughout the body in infected monkeys with the greatest concentration in the blood, bone marrow, spleen, adrenals, lymph nodes, kidney, liver, and testes, particularly in the blood-forming organs and the adrenals, as in guinea pigs. The mortality in monkeys apparently varies considerably with the strain (37, 46, 69).

(4) *Other species* Spontaneous asymptomatic infection has been described in dogs by Dalldorf (71). Ferrets, dogs, rabbits, pigs, all show virus in the blood for a short time after inoculation, but neutralizing antibodies subsequently

appear, and at no time do the animals show symptoms or fever (69) Rats may or may not show signs of infection after intracerebral inoculation (11, 69, 72) Other species which have been shown to be insusceptible are canaries, parakeets, chickens, voles, and hedgehogs (69)

(5) *Man* The disease in man, both as it occurs naturally and as a result of the inoculation of virus (infected mouse brain or blood from an infected human) has already been described

(6) *Summary* It is apparent that the virus of choriomeningitis can infect man, monkeys, guinea pigs, mice, and dogs spontaneously, although frequently the infection may be asymptomatic or only a brief febrile episode Inoculation of human beings, monkeys, mice, rats, and guinea pigs may produce a characteristic and even fatal illness in some species The distribution of the virus in the body is such as to group it with the blood-borne viscerotropic viruses Because virus is so constantly present in the blood stream there is the suggestion that blood-sucking insects may at times play a role in its transmission, but nasal secretions, saliva, and possibly urine and feces seem to be the means whereby spontaneous infection usually spreads

3 *Related viruses* A number of viruses with properties sufficiently similar to justify their consideration at this time have been described in recent years We shall present the pertinent data concerning them

(a) *The virus of pseudolymphocytic choriomeningitis* This virus was isolated in England by MacCallum, Findlay and Scott (73) from two cases of benign lymphocytic meningitis in which the cell counts of the cerebrospinal fluid were only 6 and 40 lymphocytes respectively Virus was isolated from the spinal fluid of both and the blood of one of the cases It differs from the virus of true choriomeningitis in its size of 150 to 225 millimicrons, in its inability to pass a Berkfeld X filter, and in its 4 to 5-day incubation period after the intracerebral injection of mice There is no cross immunity between the two viruses

(b) *The virus of "la maladie des porchers"* "*La maladie des porchers*," Bouchet's disease, or benign meningotyphoid of swineherds, is a specific infectious disease which has been observed for a number of years in the western part of Switzerland and the surrounding territory where the raising of pigs is an important industry (74, 75, 76) The disease occurs among those whose job it is to care for the pigs or who are exposed to their excreta (77), and usually attacks them a few weeks after they begin their duties Frequently there is a history of illness among the young pigs shortly before human cases occur The animals become groggy, lose their appetite develop distention and diarrhea, and have a symptom known as *tourniquet* a torsion of the head to one side In man the typical disease (75-76) begins suddenly with chills fever anorexia, headache, vomiting, diarrhea, distention epistaxis, prostration, and cyanosis This first stage of typhoid-like illness lasts 4 to 5 days, when a maculopapular rash appears over the lower trunk and thighs, and defervescence occurs However 36 to 72 hours later, after a period of comparative well-being, there is a sudden onset of violent headache, higher fever (104-105°), meningeal signs, and muscle pains Lumbar puncture at this time usually reveals increased pressure,

elevated protein and a marked lymphocytosis in the spinal fluid. This third stage lasts several days to a week, with a fall in temperature either by crisis or lysis. The abnormalities of the spinal fluid disappear rapidly. The third or meningeal phase may not appear at all in some patients (78).

Durand and his co-workers (79, 80) succeeded in transmitting the disease to other human beings by blood taken from a patient on the 4th day, and maintained the disease through 72 human beings by intramuscular injection of blood. They noted that the incubation period was about 8 days on the average, that the fever lasted varying periods with an average of 9 days, and that the disease rarely followed the classical pattern. Rash and meningitis were both rare in their large series. The virus, like choriomeningitis virus (49), was present in the plasma, rather than in the red cells. It passed a Chamberland L₂, but not an L₃ candle. In 3 cases out of 6 the spinal fluid contained virus. The urine was found to contain virus in the latter half of the disease and during convalescence. They also demonstrated immunity to reinoculation following the experimental disease. By intraperitoneal inoculation of blood from human cases they were able to pass the disease to a number of animal species, and then to carry it in series in these animals (81). Young pigs are susceptible and develop anorexia, diarrhea, cough, and fever. Rats, cats, and ferrets develop fever, but monkeys, rabbits, mice, and guinea pigs are quite resistant to inoculation by any route, thus differentiating this virus sharply from that of choriomeningitis.

(c) *Other viruses* (1) *Virus D*. Durand (82) has reported the isolation of a virus from his own blood during an illness characterized by an 11-day course with fever, marked constipation, loss of weight, asthenia, and insomnia. The virus was first isolated in guinea pigs, in whom it produced a fever followed by subnormal temperature for 2 days before death (mortality was 10 per cent), loss of weight, splenomegaly, and pneumonia. This is very similar to choriomeningitis infection, but Virus D produces a marked local reaction on subcutaneous inoculation in guinea pigs, which is also true of the virus of meningitis and pneumonitis of Francis and Magill (83). The virus is filtrable through Chamberland L₂ and L₃ candles, and is very stable, even being resistant to bile. It is pathogenic for monkeys, dogs, mice, hamsters, less so for rats and rabbits. The latter produce serum rich in neutralizing antibodies after inoculation. Although it produces lymphocytosis in the spinal fluid of dogs and monkeys, it never produces nervous symptoms or a fatal illness in mice, even when inoculated intracerebrally. Two patients inoculated subcutaneously developed local swelling and tenderness followed by a fever and leukopenia lasting a week. Virus was found in the blood of both and in the urine and spinal fluid of one. There was no cross-immunization with lymphocytic choriomeningitis virus.

(2) Enders and Liu (84) have recently isolated a similar virus from a patient who had a high fever lasting two weeks. The virus was isolated in guinea pigs from the patient's blood.

(3) Caminopetios and his co-workers (85) have reported the isolation of a virus from the spinal fluid of a patient with a post-vaccinal encephalitis. Rabbits, rats, mice, and monkeys were susceptible, guinea pigs resistant. The

virus produced only mild fever, minimal lesions, and immunity in inoculated animals.

(d) *Summary* It can be seen from the foregoing that there are a considerable number of similar virus agents capable of producing febrile illnesses in a wide range of animal species, occasionally localizing in the meninges to produce a rather benign form of meningitis, and transmissible by the inoculation of blood. Great care must be exercised in the laboratory to distinguish between viruses derived from the patient and viruses derived from the inoculated animals. Lymphocytic choriomeningitis virus has been found in mice, monkeys, guinea pigs, and dogs, and therefore all strains of susceptible laboratory animals to be used in experimental work should first be tested for immunity and for the presence of virus.

F. Immunity in choriomeningitis infection

1 *Natural immunity* As indicated above, certain species of animals are resistant to infection with the virus of lymphocytic choriomeningitis. These are chickens, parakeets, canaries, pigeons, cats, hamsters, and voles. In rabbits, ferrets, dogs, and pigs, infection is inapparent, but may lead to the production of antibodies. Man (32), monkeys, guinea pigs, rats, mice, and chick embryos are susceptible to infection, which may or may not be symptomatic. The factors underlying these species' differences are no more clearly understood than with other virus infections.

The so-called "interference phenomenon" has been described in connection with choriomeningitis, as with a number of other virus diseases. Dalldorf has noted (86) that when monkeys infected with choriomeningitis virus are inoculated with a very virulent poliomyelitis virus, the poliomyelitis assumes a mild atypical form, and the amount of poliomyelitis virus in the cord is much less than is usually found. Poliomyelitis infection also exerts some sparing effect on choriomeningitis infection. Brodie's finding (87) that convalescent sera from non-paralytic poliomyelitis cases would not neutralize the virus of choriomeningitis is in line with the conception that this is a non-specific phenomenon. The finding of Lagret and Durand (56) that previous infection of guinea pigs with typhus renders them refractory to infection with the choriomeningitis-like virus present in their stock mice may be another example of this so-called para-immunity (88).

As previously indicated, the sera of many individuals who have never had benign lymphocytic meningitis contain neutralizing antibodies, but since infection with the virus can be asymptomatic or produce a non-specific grippé-like disease, it is probable that these are the result of previous unrecognized infection and not due to some natural process of maturation.

2 *Acquired immunity* (a) *Immunity after infection* Animals which have recovered from previous infection with the virus of lymphocytic choriomeningitis are immune and cannot be re-infected by subsequent injections of the virus (11, 46, 60). Mice naturally infected *in utero*, that are carriers of virus in the blood and tissues, behave somewhat differently from other species. In them an

injection of any sterile irritant such as broth, starch, or a suspension of brain tissue intracerebrally, apparently produces localization of the virus, and the typical symptoms of choriomeningitis may develop (48). Mice that have recovered from contact or experimental infection after maturity are not carriers and show a solid immunity to intracerebral injection (60).

(b) *Neutralizing antibodies* are regularly found in the serum of guinea pigs (46, 60), monkeys (11, 46), dogs (27, 69, 71), rabbits (11, 29, 46, 48), and human beings (23, 32, 47), that have recovered from spontaneous infection or have been inoculated with the virus. In mice, on the other hand, the development of neutralizing antibodies has not been observed, whether there was "sterile" (no virus in blood and tissues) or "infection" immunity (virus present) (61).

The most striking characteristic of neutralizing antibodies in choriomeningitis is their slow development. At least 6 to 8 weeks are usually required for their appearance in the typical disease in man (23, 32, 89), and a similar period is required in monkeys and guinea pigs (89). Howard has reported great difficulty in demonstrating the development of antibodies in human cases from which she has isolated the virus (25, 34), but other workers do not seem to have had this difficulty. MacCallum and Findlay (28) failed to detect neutralizing antibodies in the blood of a patient with the encephalomyelitic form of the disease twelve weeks after onset. It is interesting that this patient was a carrier, from whom they were able to isolate the virus in nasopharyngeal washings taken at this time. For the time being, one should be skeptical about the causal relationship of choriomeningitis virus to a disease occurring in a patient who fails to develop specific antiviral in his blood, since infection with this virus may occur spontaneously in the laboratory animals used for its isolation.

Neutralizing antibodies may persist for several years after infection (47, 89), thus explaining their presence in the sera of 10 per cent of the general population (36). Surprisingly little is known about the chemistry of antiviral. Smadel and Wall (89) have observed the deterioration of the neutralizing power of convalescent serum stored in an ordinary icebox, but have shown that it is preserved for at least 4 years in serum dried from the frozen state. The authors have also noted the deterioration of a serum with a high titer of neutralizing antibodies during a period of 4 months. Addition of equal parts of fresh normal human serum did not restore its potency (59).

(c) *Complement fixation* by immune serum in the presence of choriomeningitis virus was first reported by Howitt (90) in a paper concerned mainly with the reaction in encephalitis. Lépine and his co-workers (91, 92) have made use of the reaction in the study of human cases of lymphocytic meningitis. Using a crude extract of infected tissue (guinea pig lung taken at the height of the infection) as antigen, they got specific increases of complement fixing power in the serum of human beings, monkeys, and rabbits recovering from infection, but for some reason were unable to get positive results with immune guinea pig serum.

Smadel and his co-workers (93, 52) have made a very complete study of complement fixation in this infection. They first showed that it was possible to separate the virus of lymphocytic choriomeningitis from a soluble antigen present

in infected tissue by differential centrifugation and Seitz filtration. The virus was sedimented from a suspension of ground infected guinea pig spleen at speeds of 20 000 to 30,000 r p m and the remaining traces of virus activity could be removed from the supernatant by Seitz filtration. The virus sediment was found to fix complement to a very slight degree while the soluble antigen in the supernatant fluid gave strong fixation.

Further studies (94) on the nature of this soluble antigen showed that it was partially concentrated in the pseudoglobulin fraction by ammonium sulfate fractionation. It withstood storage at 3°C, heat of 56°C for thirty minutes although higher temperatures inactivated it and a pH range from 4.5 to 9.0. Fresh material gave non-specific flocculation with guinea pig sera and non-specific complement fixation with human sera but after storage it was possible to obtain specific complement fixation and precipitation with mixtures of the antigen and hyperimmune guinea pig serum. Positive precipitation tests with the sera of human beings recovered from choriomeningitis infection have not been reported.

Absorption tests (94) have clearly shown that the neutralizing antibodies are distinct from those giving complement fixation. The complement fixation reaction has proved very useful in the diagnosis of the disease because of its ease of performance and the fact that it becomes positive sooner than the neutralization test (89). In man, monkeys and guinea pigs, a positive complement fixation reaction appears 3 to 4 weeks after onset whereas a positive neutralization test is not usually obtained until 6 to 8 weeks have elapsed. In rabbits, both antibodies appear somewhat earlier. In man, complement fixing antibodies disappear in the course of 4 to 6 months, while neutralizing antibodies have persisted from 6 months to 5 years. It is interesting that, although mice have never shown antiviral activity in their serum, both Traub and Schäfer (61) and Smadel and Rivers (95) have demonstrated the presence of complement fixing antibodies in the serum of hyperimmune mice.

(d) *Active immunization* Recovery from choriomeningitis virus infection produces a lasting immunity in all susceptible animal species that have been tested. Traub (96) was able to modify his virus strain by serial brain to brain passages in white mice, so that it produced only fever in guinea pigs. Within 4 days after inoculation with this modified strain, and long before the development of neutralizing antibodies in their serum, guinea pigs acquired marked resistance to the original highly virulent strain. Lyon has found that mice inoculated subcutaneously likewise become resistant to intracerebral inoculation in only 5 days (65). Subsequently Traub (97) was able to produce partial immunity in guinea pigs with formalized vaccines prepared from infected guinea pig tissues. Vaccines prepared from infected mouse tissues were ineffective although they had a higher virus content. He found that normal mouse tissue mixed with guinea pig tissue vaccine rendered it ineffectual. Repeated injections produced hyperimmunity with circulating antiviral activity in a few guinea pigs.

Smadel and Wall (89) compared the antigenic properties of their soluble antigen and virus separated by centrifugation. Suspensions of washed and

formolized virus produced both complement fixing and neutralizing antibodies and an active immunity in normal guinea pigs. On the other hand, formalin-treated virus-free extracts of infected tissue produced no complement fixing antibodies or immunity in normal guinea pigs. This soluble antigen was, however, capable of producing a marked increase in complement fixing antibodies in immune guinea pigs.

3 Summary Infection with the virus of choriomeningitis produces resistance to reinfection within a few days. In 2 to 4 weeks the animal develops complement fixing antibodies to the soluble antigen found in infected tissues, and in 6 to 10 weeks neutralizing antibodies capable of protecting other susceptible animals against infection with the virus. Mice are exceptions in that neutralizing antibodies are never found in their blood or tissues. In man, both types of antibody appear in response to infection, although the appearance of neutralizing properties in the serum may be delayed for many weeks. While complement fixing antibodies usually disappear within 6 months, neutralizing antibodies may last a number of years. Active immunization has been possible in guinea pigs with formolized guinea pig virus.

G Pathology

1 Animals In the chick embryo, infected at 11 days by inoculation on the chorio-allantoic membrane, the disease is frequently fatal. Lillie (98) has noted very minor non-specific lesions in the viscera and membrane, with the most striking finding "an increased tendency to maturation of myeloid collections toward polymorphonuclear leukocytes."

In mice (11, 15, 27, 29, 46, 69), the lesions vary somewhat with the route of inoculation. Following intraperitoneal inoculation, particularly with a strain freshly isolated from mice, the most extensive lesions are visceral, and consist of pallor of the liver, bronchopneumonia, and frequently pleural, pericardial, and peritoneal exudates (16, 59). On section the liver shows capillary engorgement, small areas of necrosis, increase and swelling of the Kupffer cells, and infiltrations of lymphocytes, monocytes, plasma cells, and some polymorphonuclear leukocytes. The bronchopneumonia is of the interstitial type, and the exudates that may be found in the serous cavities show lymphocytes and large mononuclear cells. Other organs show comparatively little change. Following intracerebral inoculation, the striking lesions are confined to the central nervous system, but changes in the liver may be present and interstitial pneumonia is usually observed. Macroscopically the brain shows only congestion but microscopically there is a marked infiltration of mononuclear cells into the meninges, ventricles, and choroid plexus. The meningeal changes are most marked at the base of the brain. Perivascular cuffing in the brain substance is rarely found, unless the animals are killed several weeks after recovery.

In rats inoculated intracerebrally, the changes are very similar to those found in mice, although usually they are less prominent (29, 46). Findlay and Stern report more polymorphonuclear leukocytes in the exudate than with other species (69).

In guinea pigs lesions of the lungs predominate while the meningeal reaction is minimal even after intracerebral inoculation (15, 17, 46 69) Some round cell infiltration of the meninges and ventricles is found but the striking change is the extensive interstitial bronchopneumonia and the marked emaciation of the animal

In monkeys the pathology seems to depend as in mice on the type of infection In a highly virulent epizootic among his stock monkeys due to this virus Coggeshall (68) reported purely visceral lesions consisting of bronchopneumonia and pleural and pericardial effusions Findlay and Stern (69) observed pleural effusion in a monkey inoculated intraperitoneally Microscopic visceral lesions in monkeys consist of round cell infiltrations in the liver kidneys adrenals lungs, heart muscle and pancreas Congestion and hemorrhagic consolidation of the lungs and focal necrosis in the liver are often found Swelling and hyperplasia of the reticulo-endothelial cells of the spleen liver and lymph nodes are usually seen Most studies have been made on intracerebrally inoculated animals and in them visceral lesions though present are overshadowed by the characteristic choriomeningitis which gives the infection its name (11 15 46 69 99) The choroid plexus shows a dense infiltration of mononuclear cells between the walls of the choroidal vessels and the surrounding ependymal layer producing a marked increase in size of the villi The involvement of the meninges is usually less striking but present It is the contrast between the extensive involvement of choroid plexus and meninges and the minimal lesions within the brain substance itself which makes the pathology of this infection so different from that of other virus infections of the central nervous system

Inclusion bodies have not been observed by most workers (11 46 99) However Dalldorf (71) felt that he could diagnose infection with choriomeningitis virus in the dog by the finding of intranuclear inclusions in the cells of the adrenal cortex Similar inclusions were also noted in the adrenals of ferrets mice and guinea pigs This finding is suggestive in view of Mendoza's finding (67) of large amounts of virus in the adrenals of guinea pigs Findlay and Stern (69) found intranuclear inclusions in the choroid plexus of mice, but came to the conclusion that they were due to mouse salivary gland virus, since they were also found in control mice These authors recorded the presence of minute granules in the cytoplasm of mononuclear cells in the ventricular exudate of monkeys, rats and mice The granules were clearly seen when stained with Giemsa and observed with the dark field microscope Smadel (52) and his co-workers were able to obtain somewhat similar granules in the high speed centrifugates of virus suspensions

2 Man The pathology of choriomeningitis infection in man is not definitely known since no clearly proved cases have come to autopsy Viets and Warren (100) reported a fatal case of acute lymphocytic meningitis in 1937 No virus studies were made They found infiltration of the meninges with lymphocytes and considerable perivascular infiltration in the brain substance In the mid-brain region the ganglion cells showed evidence of damage with nuclei pyknotic and cytoplasm filled with small inclusion bodies Silcott and Neubürger (101)

have reported three fatal cases recently, in none of whom virus studies were made. Clinically these cases were not typical, but might have represented choriomeningitis infections in old people. All three showed a patchy lymphocytic infiltration of the meninges, nodular gliosis, and perivascular cuffing, particularly in the midbrain area.

The most convincing case report is that of Machella, Weinberger, and Lippincott (102) of a 14-year-old boy who had a story quite compatible with lymphocytic choriomeningitis, with a prodromal illness and a remission before the onset of meningeal symptoms. Two guinea pigs inoculated with spinal fluid died on the 16th day with congestion of the lungs and enlarged spleen. The ground lungs and spleens were filtered, and a guinea pig inoculated with the filtrate died on the 17th day with similar findings. Unfortunately, no further attempt to identify the virus was made, but these findings are consistent with choriomeningitis in guinea pigs. The authors strengthen their case by noting that no other deaths occurred among guinea pigs in their stock inoculated with other material.

Their patient apparently was well on the way to recovery, when he developed evidence of subarachnoid block on the 28th day and died of respiratory failure. The findings at post-mortem were consistent with the findings in monkeys, but showed more scarring due to the longer course before death. There were marked inflammatory changes in the walls of the ventricles, where the ependyma was denuded, with lymphocytic infiltration, glial proliferation, and engorgement of vessels. The choroid plexus was thickened, scarred, and infiltrated with lymphocytes, and there was an intense inflammatory reaction of the meninges, with scarring and obliteration of the subarachnoid space at the base of the brain. In the fourth ventricle the process caused softening which involved the adjacent nuclei. The authors commented on the striking contrast between the intense inflammation of meninges, ventricular walls, and choroid plexuses and the normal appearance of the brain substance.

The marked scarring in this case 5 weeks after onset is interesting in the light of the report of Barker and Ford (24) of a patient who had proven lymphocytic choriomeningitis and developed paraplegia due to an obliterative arachnoiditis 4 months later.

Other deaths have been reported by Tassinari (103) and by Howard (34). The latter has presented data which are difficult to interpret and should be taken as a stimulus to further research, rather than as proven fact until confirmed. In a series of 33 patients admitted with a variety of infections involving the central nervous system, she isolated the virus of choriomeningitis in 8. The first 6 cases had histories more or less typical of the disease, and isolation of the virus from the spinal fluid in each case was accomplished by guinea pig inoculation. Adequate proof that this was the virus of lymphocytic choriomeningitis was brought forward. One of these cases had the encephalomyelitic form of the disease, and died suddenly 4 months after onset in a State Hospital, but no autopsy was performed. The seventh and eighth cases studied by Howard are provocative, since they represent cases of severe encephalitis, fatal in 9 and 12 days. Virus could not be isolated from the spinal fluid despite the presence of

over 1000 cells in each case, but was isolated from brain tissue kept under glycerine 70 days. In one case the isolation of the virus was fairly convincing, but in the other case, 14 weeks elapsed after inoculation before the guinea pig succumbed, and the possibility of spontaneous infection must be considered. In one case, post-mortem examination revealed marked focal lesions in the substantia nigra and a transverse myelitis. In the other there was meningeal, but not choroidal, infiltration, and massive necrosis in the cerebrum with endothelial proliferation so marked that vascular occlusion and hemorrhagic necrosis of the brain were observed. It is interesting that in both cases a systemic prodromal illness occurred which simulated "grippe" and resembled the prodromal illnesses in some of the first 6 cases.

3 Summary The pathology of lymphocytic choriomeningitis infection in animals bears anatomical testimony to the generalized nature of this infection. Infiltrations of lymphocytes, plasma cells, and large mononuclear cells are widespread in many organs. Reticuloendothelial hyperplasia is frequently seen. Interstitial bronchopneumonia is frequent, and polyserositis not uncommon. Choriomeningitis of mild degree may occur frequently, but is rarely marked unless intracerebral inoculation is practiced.

In the light of these findings, it is interesting to speculate on the pathology produced by this virus in man. One fatality in man fits the pattern of infection as it is observed in animals. Other fatal cases raise the question of whether severe encephalitis with abundant lesions in the brain substance may occur. The studies in animals suggest above all that systemic forms of infection should be far more frequent than cases involving the central nervous system. Respiratory disease characterized by constitutional symptoms, interstitial pneumonia, and pleural effusion is to be expected in the light of comparative pathology. Clinical investigation of this disease should turn to a study of its relationship to cases of so-called atypical or virus pneumonia, unexplained pleurisy with effusion, and fever of unknown origin, as well as to its rôle in encephalitis.

H Epidemiology

Following the description of human cases of lymphocytic choriomeningitis in 1935, numerous speculations concerning the epidemiology of this disease were made. There was a repeated suggestion that mice might play a rôle in human infections. Several cases of lymphocytic choriomeningitis among laboratory workers who had been in contact with virus-carrying white mice had been observed. In addition, a possible reservoir of infection in the common grey mouse (*mus musculus*) had been suggested by several clinical observations. During the past two years a grey mouse reservoir for a series of human cases of this virus disease has been established. The evidence to support this view, that human cases of lymphocytic choriomeningitis are infected from virus-carrying grey mice will be presented in detail.

1 The rôle of white mice in human laboratory infections In 1935 Traub (17, 22) isolated the virus of lymphocytic choriomeningitis from the blood and urine of apparently healthy white mice. This virus was transmitted from preg-

nant mice to their offspring, and after recovery from the infection the young mice carried the virus for several months. The possibility that these virus-carrying mice might infect human beings was suggested by the demonstration of neutralizing antibodies in the serum of J. M., who had been the caretaker of this infected mouse colony for 5 years. In substantiation of this view, Rivers and Scott (46) reported a patient with lymphocytic choriomeningitis, who had worked with a stock of virus-infected, white mice during the 3 months before his illness. Although they suggested that the patient had probably infected the mouse colony, the possibility of mouse-to-man transmission was not excluded.

Experimental studies have shown that the virus is capable of readily adapting itself from a white mouse to a human host (13). When virus-infected brain emulsions from white mice are inoculated into human beings, lymphocytic choriomeningitis may be produced.

These observations suggest that an occasional laboratory infection may be related to contact with virus-carrying white mice. However, white mice are certainly not the source of clinical cases of lymphocytic choriomeningitis, for most patients report that they have never seen a white mouse.

2 *The rôle of grey mice in the transmission of lymphocytic choriomeningitis*
In 1936 Traub (35) showed that intracerebral injections of the virus into grey mice produced the same fatal clinical picture as in white mice. After subcutaneous inoculations, grey mice carried the virus for several weeks.

Two cases of lymphocytic choriomeningitis with histories suggestive of possible transmission from grey mice were described in 1936. The first case was reported by Findlay, Alcock, and Stern (27). In relating the history of this patient, the authors noted "that some days before the onset of his illness, he had cleared out a shed, which was heavily overrun with mice." Collis (104) described a second patient, whose clinical picture was consistent with lymphocytic choriomeningitis, and whose serum after recovery neutralized the virus. "This patient lived in an eighteenth century house overrun with rats and mice" (27). In these two reports the possible rôle of grey mice in the epidemiology of this virus infection was suggested for the first time. This observation, that cases of lymphocytic choriomeningitis occur in homes inhabited by grey mice, was in itself not too significant, for a large percentage of homes are so inhabited. A more important point to be established was the fact that the mouse inhabitants of these homes were actually carrying the virus.

In 1939 and 1940 Armstrong and his co-workers (16, 57, 58) demonstrated the existence of virus in grey mice caught in the homes of 5 of 6 patients with lymphocytic choriomeningitis. These cases represented consecutive ones studied over a period of 17 months. Five patients lived in or near Washington, D. C., each one in a different section of the city, while the sixth lived in Lancaster, Pa. The virus of lymphocytic choriomeningitis was recovered from the cerebrospinal fluid of 5 of the 6 cases, while in one case no fluid was obtainable for study (Table 5, Cases 1 to 6).

In all 6 patients, protective antibodies developed in the blood after recovery. Grey mice trapped in 5 of the homes were shown to harbor the virus in their

viscera while mice trapped in the sixth home were found not to be infected Haas (64) observed 7 of these naturally-infected grey mice in his laboratory for 5 months During this time the mice showed no outward signs of infection although the virus was recovered from their blood and feces several times

The percentage of mice carrying the virus in an infected home was investigated extensively by Armstrong He trapped grey mice in 78 different homes in Washington and found that 35 of these homes harbored infected mice From these 35 infected homes 123 mice were examined and 53 per cent of them were found to be carriers of active virus In sharp contrast with these findings, the virus was not isolated from a single one of 184 mice trapped in the other 43 homes These findings were verified by testing another series of grey mice for immunity to intracerebral inoculations of lethal doses of the virus Of 62 mice trapped in 22 homes where virus-infected mice had been found 66 per cent were immune in contrast to 10 per cent of 47 mice trapped in homes where only non-infected mice

TABLE 5
Mouse reservoir of Lymphocytic choriomeningitis

CASE	VIRUS ISOLATED FROM STRAW PLANT	ANTIBODIES DEVELOPED IN SERUM	VIRUS ISOLATED FROM GREY MICE AT PATIENT'S HOME	ESTABLISHED DIAGNOSIS
1 Ref 57	—	—	+	Lymphocytic choriomeningitis
2 Ref 57	—	+	+	Lymphocytic choriomeningitis
3 Ref 58	—	+	—	Lymphocytic choriomeningitis
4 Ref 58	—	—	+	Lymphocytic choriomeningitis
5 Ref 16	—	—	—	Lymphocytic choriomeningitis
6 Ref 16	—	—	0	Lymphocytic choriomeningitis
7 E A	—	—	+	Lymphocytic choriomeningitis
8 V M	0	—	0	Infectious mononucleosis
9 A C	0	0	0	Acute aseptic meningitis etiology unknown

had been found These studies indicate that if a home is inhabited by infected mice 50 to 60 per cent of the mice in that particular home will probably be carrying the virus In contrast with this a large percentage of mouse-inhabited homes do not contain infected mice Thus the mouse reservoir of the virus is concentrated in small areas and it is not evenly distributed throughout the mouse population

The association of virus infection in mice with human cases of lymphocytic choriomeningitis was established by Armstrong (Table 5 Cases 1 to 6) The 35 virus-infected homes which he studied included 5 homes in which human cases of lymphocytic choriomeningitis had occurred However in the 43 homes in which no virus-infected mice had been found only one case of lymphocytic choriomeningitis had developed In this latter case the home had been overrun with mice and the patient had trapped a dozen mice before his illness However, the two mice which the investigators trapped were not carrying the virus

The authors have confirmed Armstrong's findings in an epidemiological study

of E A, a patient with lymphocytic choriomeningitis⁶ In this case the diagnosis was established by the isolation of the virus from the patient's cerebrospinal fluid, and by the demonstration of complement-fixing and neutralizing antibodies in her serum after recovery Of 7 mice trapped in her home, 4 were carrying the virus⁷ In contrast with this, 30 mice were trapped in homes and buildings in other parts of Boston and vicinity by the authors, and none of these mice was infected with the virus In addition to this study, Yamarat (40) trapped 68 mice in various parts of Boston with no relation to human cases of lymphocytic choriomeningitis, and he found only 3 mice which were virus-carriers Thus, the incidence of virus-infection among mice in Boston is approximately 4 per cent However, at the home of a case of lymphocytic choriomeningitis, 50 per cent of the mice were carrying this virus

Thus it has been established and confirmed that a close association exists between human cases of lymphocytic choriomeningitis and a mouse reservoir of the virus In contrast with this positive relationship are the negative epidemiological studies of two cases with lymphocytic reactions in the cerebrospinal fluid, not due to the virus of lymphocytic choriomeningitis, studied by the authors In each of these cases a history of exposure to mice was elicited, and the diagnosis of lymphocytic choriomeningitis was entertained, but the wild mice were not found to harbor the virus

Patient V M (Table 5, Case 8),⁸ a student nurse, developed fever, headache, and a slightly stiff neck, with 12 lymphocytes per cu mm. in the cerebrospinal fluid Prior to her illness she had been working in a building infested with mice Three weeks before the onset of headache and fever, she had reset the cheese in a mouse trap With this suggestive story, 3 mice were trapped at her place of work, but none of them was carrying the virus Cerebrospinal fluid, drawn from the patient at the onset of meningitis, was inoculated into mice and guinea pigs with negative results Her subsequent course and laboratory findings were typical of infectious mononucleosis

Patient A C (Table 5, Case 9) developed headache, fever, chills, and stiff neck, with 384 lymphocytes per cu mm in the spinal fluid Inoculations of his spinal fluid, blood, mouth washings, urine, and feces into mice and guinea pigs at the onset of meningitis, showed no evidence of the virus of lymphocytic choriomeningitis He did not develop complement fixing or neutralizing antibodies against the virus during convalescence Since the apartment in which the patient lived, and the antique factory where he worked were both overrun with mice, epidemiological studies were undertaken Four mice were trapped in his home, and 12 additional mice in the factory None of these was carrying the virus

These negative epidemiological findings are of definite significance The 2 patients presented the clinical pictures of "acute aseptic meningitis," and their homes or places of work were inhabited by mice However, the mouse inhabitants were not carrying the virus of lymphocytic choriomeningitis, and the patients were not infected with the virus In the first case, the diagnosis of infectious mononucleosis was established, whereas in the second case the etiology remains unknown

⁶ The clinical history of this patient is presented on pages 7-15

⁷ See appendix, p

⁸ A resume of the clinical chart of this patient is presented on page 93

Additional positive evidence in favor of the close relationship between human cases of lymphocytic choriomeningitis and a virus reservoir in mice is suggested by the discovery of an endemic focus of human virus infection by one of the authors. Among the negroes in Boston, only 4 cases of this disease have been observed in the larger hospitals during the past 8 years. These cases (which in-

MAP 1 AN ENDEMIC FOCUS OF LYMPHOCYTIC CHORIOMENINGITIS

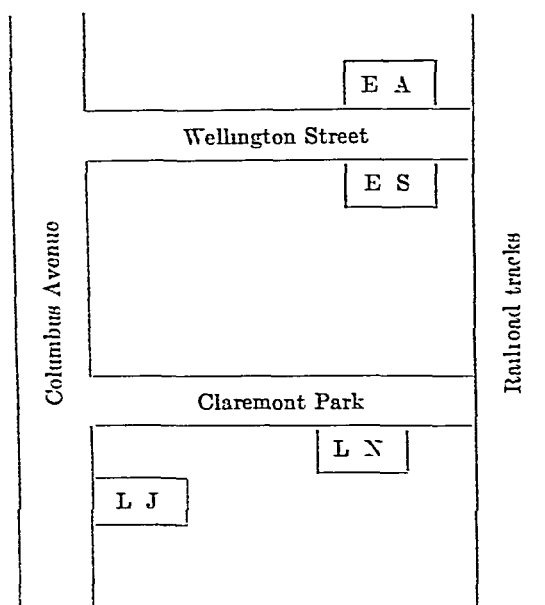


TABLE 6

An endemic focus of lymphocytic choriomeningitis associated with a mouse reservoir of the virus

NEGRO PATIENTS	YEAR OF ILLNESS	EVIDENCE FOR DIAGNOSIS	POSSIBLE MODE OF TRANSMISSION
1 E A	1940	Clinical, virus isolated, antibodies present	Mouse contact
2 L N (Ref 105)	1940	Clinical, antibodies present	Mouse contact
3 L J	1934	Clinical, no antibodies present in 1941	Patient unreliable
4 E S	1933	Clinical, no antibodies present in 1941	Mouse contact

clude the patient E A, described above) are summarized in Table 6. The unusual finding is that all 4 of these colored people, at the times of their illnesses, were living within 2 city blocks of each other (Map 1). Since there are 20,000 negroes in Boston, this concentration of cases is an unusual coincidence. At the present time it is known that this small section of the city contains a mouse

reservoir of the virus. In addition, the observation that the embryos of an infected grey mouse caught in the cellar of the home of the patient E. A. were highly potent carriers of the virus, shows that the virus is passed from mouse generation to the next by intra-uterine infection, and suggests that the mouse reservoir may be a very old one.

These studies show that a close relationship does exist between human cases of virus infection and an associated mouse reservoir of the virus. The question is whether the infection is transmitted from mice to human beings or from human beings to mice.

Although one cannot prove definitely at present that the natural disease is transmitted from mice to man, the evidence points in this direction. Four cases of laboratory infections have been reported in workers who had handled infected mice. This circumstantial evidence certainly suggests mouse-to-man transmission. The sequence of events in the illness of the patient E. A. further substantiates this view. She took a mouse from a trap and handled this mouse 20 days before the onset of meningitis. Mice trapped both in her fourth floor apartment and in the cellar of her home were carrying the virus at the time of her illness. The interval from mouse contact to the development of meningitis in this case is the same as the experimental incubation period of the disease. It appears more probable that she was infected by a mouse carrier than that she infected the mice in the building. In addition, it is quite remarkable that 3 other people in this neighborhood should have experienced the same infection in previous years.

The available evidence suggests that in a number of cases of lymphocytic choriomeningitis the virus was transmitted from mice to humans. Experimental work has demonstrated that grey mice carry the virus in their feces, urine, and blood. By inference from experiments on white mice, it is probable that the semen and saliva of infected grey mice also contain virus. Thus there is an abundant source of virus in the excreta of these animals. The possible methods by which this virus might be transmitted to man are as follows:

- 1) Direct contact with dead mice. The patient E. A. was the first case of lymphocytic choriomeningitis in which there was significant evidence to show that infection might have occurred by mouse contact. In a review of the other 3 cases in the same neighborhood as this patient, 2 histories of mouse contact were obtained, while the third patient was completely unreliable (Table 6). This circumstantial evidence suggests that contact with the virus-infected blood, feces, or other excreta of a recently killed mouse may be the mode of transmission in some cases.

- 2) The eating of food contaminated by infected mouse excreta. No evidence is available.

- 3) The inhalation of dust contaminated by mouse excreta. No evidence is available.

- 4) The bites of an insect vector. No evidence is available.

In summary, it is possible that in some cases the virus is transmitted from mouse to man by direct contact with a recently trapped, infected mouse, and in

particular with his excreta. In other cases the mode of transmission from mice to human beings is unknown.

3 *The possible transmission of the infection from dog to man* The following case study by one of the authors presents circumstantial evidence to show that the virus might be transmitted from dog to man.

J. K. (Boston City Hospital No. 96930S), a 23-year-old, white single girl, was admitted as a private patient to the Boston City Hospital, Boston, Mass. on November 17, 1939. She complained of headache, vomiting and fever of 2 days' duration. Seven days before the onset of meningitis she had been sick with fever and headache, but had recovered temporarily. The cell count in the cerebrospinal fluid reached a maximum of 1095 white blood cells per cu. mm., all lymphocytes. The meningitis and fever lasted 15 days, followed by complete recovery. The diagnosis of lymphocytic choriomeningitis was established by the development of neutralizing antibodies in her serum. During the past 18 months she has remained perfectly well.

The patient, who lived in the environs of Framingham, Mass., had never seen a mouse in her home and she had never touched a mouse in her life. Three cats were kept at home to catch any mice which might appear, but the patient did not handle the cats. In brief, there was no evidence at all of mouse inhabitation. However, an interesting observation was made by the patient. Her dog had fallen ill about 3 weeks before she went to the hospital, and the veterinarian had made the diagnosis of canine distemper. About 3 days before the patient went to the hospital, the dog was removed to the veterinary hospital, where it died 10 days later.

This history presents a striking coincidence. The patient developed an infection with the virus of lymphocytic choriomeningitis shortly after the onset of a fatal illness in her dog, which the veterinarian diagnosed clinically as canine distemper. The patient handled this sick animal prior to her own illness. This contact with a distemper dog is particularly suggestive in the light of the experimental work of Dalldorf and Douglass (71, 106). They recovered the virus of lymphocytic choriomeningitis from 4 samples of dog spleen which contained the virus of canine distemper. They showed that these 2 viruses had been present simultaneously in their source material for more than $2\frac{1}{2}$ years. It was not known how the virus of lymphocytic choriomeningitis was introduced into the passage virus. When another strain of distemper virus, which was demonstrated to be free from the virus of lymphocytic choriomeningitis, was introduced into the laboratory, it too was soon contaminated with the virus of lymphocytic choriomeningitis. When it is injected subcutaneously into dogs, the virus of lymphocytic choriomeningitis produces no clinical illness, although specific antibodies appear in the blood serum within 35 days. Furthermore, an inoculated dog transmits the infection to his cage mate. Thus, if dogs in nature do become infected with the virus of lymphocytic choriomeningitis, they can readily transmit it.

Meyer in his Harvey Lecture (107) reported that Howitt in California had isolated a virus closely related to or identical with choriomeningitis virus from 3 dogs. These animals died of an ascending myelitis and pathologic studies re-

* The clinical history of this patient has been reported by Dr. H. H. Merritt (105).

vealed an intense inflammatory process in the cord. The relationship of the virus of choriomeningitis to the disease was unknown. The finding is important, because it means that a choriomeningitis-like virus has been isolated from dogs in the field as well as in the laboratory.

4 *The transmission of the virus from guinea pigs to man* Two laboratory infections with the virus have been traced to guinea pigs. One case of lymphocytic choriomeningitis (33) followed the accidental, conjunctival inoculation of virus contained in an organ emulsion from a guinea pig. The second case (35) was an inapparent infection in a laboratory worker who had handled virus-infected guinea pigs.

5 *A reservoir of the virus in monkeys* Spontaneous infections in monkeys with the virus have occurred, and a few individuals in contact with infected monkeys had had neutralizing antibodies against the virus in their blood. However, no case of monkey-to-man transmission of the disease has been reported.

6 *The possibility of man-to-man transmission of the virus* Although the evidence is too fragmentary to be conclusive, this virus is probably not transmitted from man-to-man. There are no recorded instances of one patient contracting lymphocytic choriomeningitis from another. However, it might be argued that most contacts are not susceptible individuals, or that they develop inapparent infections with the virus, followed by immunity. The authors have shown that this did not occur in the contacts of the patient E. A. Sera from 5 individuals who were in close contact with the patient during her hospital stay, were studied. From each person 2 sera were drawn, the first at the beginning of exposure, and the second 2 months later. These sera were examined by the mouse-protection test for the possible development of neutralizing antibodies, but none of the individuals developed any anti-virus. During the 2 months' period, all 5 individuals remained well and had no symptoms suggestive of a meningeal or non-meningeal form of virus infection.

Lépine, Mollaret, and Kreis (32) have reported one case of experimental transmission of the virus from man-to-man. In this case they wrote "we have been able to reproduce the febrile disease by the intramuscular inoculation of 25 cc. of blood from a sick patient." No further information concerning this experiment is available.

In 1937 Armstrong (36) mentioned the possibility of a venereal route for human-to-human infections. This was suggested by the higher incidence of protective antibodies in the sera of individuals over 16 years of age, and in the sera of several prison groups with a high percentage of positive Wassermann reactions. It was supported by the finding that infection took place in monkeys after the instillation of lymphocytic choriomeningitis virus into the urethra or vagina. However, there has been no clinical verification of this possibility.

7 *Experimental transmission of the virus by insects* Coggeshall (68) has shown that infected *Aedes aegypti* mosquitoes can transmit the virus to guinea pigs by their bite. The tick, *Dermacentor andersoni*, Stiles, can also be experimentally infected with the virus, and the adult form may carry the virus as long as 13 days. Shaughnessy and Milzer (108) have demonstrated that infected tick feces and crushed ticks applied to the scarified skin of a guinea pig will transmit

the disease. However it appears unlikely that insects are vectors in the transmission of this disease to man in view of the seasonal incidence of cases of lymphocytic choriomeningitis in the north temperate zone. In the summer when these insects are most plentiful no cases of infection have been reported.

8 *The possible portals of entry of the virus in man.* Although the portal of entry of the virus is not known the experimental and clinical evidence in favor of various routes of infection will be summarized.

(a) *Subcutaneous route.* If a mouse strain of the virus is injected subcutaneously in man it may produce lymphocytic choriomeningitis. No local skin reaction occurs at the site of injection. At the present time there are no clinical observations to establish this subcutaneous portal of entry.

(b) *Intracutaneous route.* Shaughnessy and Zichis (109, 66) have shown that the virus passes through the unbroken skin of the guinea pig and produces infection. It is not known whether this occurs in man.

(c) *Conjunctival route.* One laboratory infection occurred after the accidental inoculation of virus in the conjunctival sac (33). However no other clinical cases have been reported in which a conjunctival portal of entry was suggested.

(d) *Respiratory tract.* The precursory symptoms of lymphocytic choriomeningitis frequently include an upper respiratory infection. Kreis (13) noted the development in a patient of cough and bronchitis during the prodromal phase of an experimental infection with the virus. However an attempt to isolate the virus from the mouth washings of this patient gave negative results. The authors were unable to obtain the virus from the mouth washings of the patient E. A. during the meningeal phase of her illness. The virus has never been isolated from mouth washings during the prodromal or the meningeal phase of this disease but in one case it was obtained from mouth washings taken during the convalescent stage (28). The first studies of the mouth washings of this patient were made 2 months after the onset of illness at which time the virus was isolated by the inoculation of a monkey. One month later the virus was again found in the mouth washings by guinea pig injections. None of this evidence can be taken as proof of a respiratory portal of entry. Recently Findlay has reported a case of proved choriomeningitis which occurred in a soldier in a ward where an epidemic of respiratory infection was going on (19).

(e) *Alimentary tract.* No evidence is available.

In brief the portal of entry of this virus in man remains a mystery in many cases, but penetration of the unbroken skin or conjunctiva or infection by way of the alimentary or respiratory tracts would be expected on the basis of our present knowledge of the disease.

I Differential diagnosis

The systemic illness produced by the virus of lymphocytic choriomeningitis is a grippelike infection which may be diagnosed clinically as a cold. In an epidemic period the diagnosis of influenza might be made. Unless a virus is isolated from the patient or neutralizing antibodies are demonstrated in his serum after recovery no etiological diagnosis is made.

If the patient develops fever, headache, nausea, vomiting and a meningeal re-

action, this symptom-complex presents the differential diagnosis of a fever of unknown etiology. Tuberculosis, typhoid fever, brucellosis, subacute bacterial endocarditis, and infectious mononucleosis are among the possibilities. An acute infection, such as pneumonia, with meningismus, is to be considered. However, the finding of a lymphocytic reaction in the cerebrospinal fluid on lumbar puncture limits the diagnosis to those diseases which produce such a mononuclear response. Among these infections, tuberculous and syphilitic meningitis are usually considered first.

1 Acute tuberculous meningitis This fatal illness usually commences with headache, nausea, lassitude, and fever, lasting a week or more. By the second week, stiff neck, squint, facial weakness, or dysarthria may be observed. This picture is followed by stupor, muscular twitchings, paralysis, and death. The duration of illness is usually about 3 weeks, although the clinical course is occasionally atypical.

The cerebrospinal fluid is usually under increased pressure and is clear or opalescent. A web-like clot usually forms on standing. The cell count varies from 50 to 500 cells per cu mm, about 80 per cent of which are lymphocytes and 20 per cent are polymorphonuclear cells. The protein content is increased (45 to 500 mgs per 100 cc). The sugar content is decreased below 45 mgs per 100 cc, and the chloride content is likewise diminished below 650 mgs per 100 cc. The colloidal gold reaction may be of any type, and the Wassermann reaction is negative (110). The diagnosis is established by the demonstration of tubercle bacilli on smears of the cerebrospinal fluid or by the results of guinea pig inoculations.

Although the occasional finding of a tuberculous process elsewhere in the body is very suggestive evidence, usually the early diagnosis of tuberculous meningitis cannot be made from the history and physical examination. However, the chemical findings in the spinal fluid form a syndrome, which rarely occurs in any other disease. In a lymphocytic fluid the sugar content is decreased along with a reduced chloride level. In contrast with these findings, the spinal fluid in cases of lymphocytic choromeningitis has a normal sugar and chloride content, and the cells are 90 to 100 per cent lymphocytes. In tuberculous meningitis the blood sedimentation rate is elevated, whereas in lymphocytic choromeningitis the sedimentation rate is normal. The final diagnosis is established by appropriate bacteriological methods.

2 Acute syphilitic meningitis Meningitic symptoms may develop at any stage of luetic infection, but they are usually a manifestation of secondary syphilis. A history of syphilis may be obtained, the scar of a healed primary lesion may remain, or a secondary skin rash may be present. The symptoms of headache, fever, insomnia, weakness, and pain in the back or neck develop. These are followed by cranial nerve involvement with tinnitus, deafness, vertigo, facial weakness, or squint. The cerebrospinal fluid is usually under increased pressure, with an average of 500 cells per cu mm, most of which are lymphocytes. The sugar and chloride contents are usually normal. The colloidal gold reaction is nearly always abnormal, and the Wassermann reaction is positive. Thus the

etiological diagnosis is suggested by the clinical history and established by the Wassermann reaction. In lymphocytic choriomeningitis, the Wassermann reaction is negative, and the specific virus may be isolated by appropriate methods.

S. Virus infections of the central nervous system. A number of virus diseases affecting the nervous system have been studied, and their clinical pictures are usually distinctive. However, just as the virus of lymphocytic choriomeningitis may produce atypical signs and symptoms, so other viruses produce aberrant illnesses, which in some cases simulate infection with the virus of lymphocytic choriomeningitis.

(a) *Anterior poliomyelitis* may be confused with lymphocytic choriomeningitis. In the premonitory stage of poliomyelitis, which occurs in 95 per cent of the cases, the child may have fever, headache, coryza, sore throat, anorexia, nausea, vomiting, and diarrhea. He resents any disturbance, and on examination usually has some rigidity of the neck or spine, frequently with muscle tenderness. This prodromal phase is much shorter than that found in lymphocytic choriomeningitis, although the same remission of symptoms before the second phase of the disease may occur in both virus infections. In paralytic poliomyelitis the child suddenly becomes ill again with the onset of headache, fever, and muscular paralysis. The cerebrospinal fluid findings in these 2 diseases may be identical, although in an early case the predominance of polymorphonuclear leukocytes favors the diagnosis of poliomyelitis. If paralysis does not develop, the infection may be either non-paralytic poliomyelitis or lymphocytic choriomeningitis. However, the occurrence of such an illness in a child during the late summer months, concomitant with an epidemic of poliomyelitis in the community, with a rapid diminution in the number of cells in the spinal fluid, certainly suggests the diagnosis of non-paralytic poliomyelitis.

If a child develops paralysis after a prodromal illness, the diagnosis of poliomyelitis appears certain, although the slight possibility of infection with the virus of lymphocytic choriomeningitis does exist. MacCallum and Findlay (28) described such a case. A young girl had the precursory symptoms of aching in the calves, thighs and lumbar back, associated with the sensation of pins and needles from her umbilicus to her toes. After the onset of headache and fever, she developed a flaccid paralysis of both legs. The spinal fluid revealed 101 cells per cu mm. Four months after this infection the patient still had complete paralysis of both lower extremities with muscle atrophy. A clinical diagnosis of anterior poliomyelitis was made at the onset of paralysis. However, the virus of lymphocytic choriomeningitis was isolated in guinea pigs from the patient's spinal fluid, drawn on the 7th day of central nervous system involvement.

(b) *Mumps* is frequently accompanied by a meningeal reaction. The symptoms, signs, and cerebrospinal fluid findings may be identical with those of lymphocytic choriomeningitis. In such cases the clinical diagnosis of mumps meningitis is made on the basis of the concomitant parotitis, orchitis, or pancreatitis. The meningeal reaction may precede or follow these somatic signs of infection, and in some cases it may occur as a purely meningeal illness.

(c) *Herpes zoster.* Occasionally a mild meningeal reaction may precede the

onset of *herpes zoster* In these cases the lymphocytic reaction in the spinal fluid may be the same as that found in lymphocytic choriomeningitis (111, 112) However, with the outbreak of herpetic vesicles, the diagnosis is established

(d) *The encephalitides* Several viruses produce encephalitis in human beings, and the clinical pictures of these disease are usually characteristic (113) *St Louis encephalitis* occurs in 3 clinical forms an acute onset of encephalitis, a short prodromal phase followed by encephalitis, and an abortive form In addition to meningeal signs, the patient usually develops lethargy, mental confusion, and tremors The cerebrospinal fluid findings may be identical with those of lymphocytic choriomeningitis However, the isolation of the virus or the demonstration of neutralizing antibodies in the patient's convalescent serum establishes the diagnosis *Post-infection encephalomyelitis* occasionally occurs during convalescence from infectious diseases, particularly those caused by viruses, after vaccination, or after prophylactic inoculations against rabies *Epidemic encephalitis* of unknown etiology may also present a clinical picture and cerebrospinal fluid findings similar to the encephalomyelitic form of lymphocytic choriomeningitis However, no etiological diagnosis can be made *Equine encephalomyelitis* usually produces a predominantly polymorphonuclear reaction in the early spinal fluids, and the patients usually appear much sicker than with choriomeningitis (114)

(e) *La maladie des porchers* is a virus disease which occurs occasionally among individuals working in contact with virus-infected pigs The disease has been reported in France, Switzerland, and Italy, but it has not been encountered in the United States This illness has a characteristic clinical course, which includes two febrile waves separated by a period of apyrexia The meningeal symptoms are acute, with a lymphocytic cellular reaction in the spinal fluid A maculopapular eruption usually appears and lasts a few days Conjunctivitis frequently occurs This virus, isolated by Durand and his co-workers (79, 81) is not related serologically to the virus of lymphocytic choriomeningitis

(f) *Pseudolymphocytic choriomeningitis* The virus of pseudolymphocytic choriomeningitis has been isolated in England from the cerebrospinal fluid of 2 patients with the clinical picture of acute aseptic meningitis (73) This virus can be distinguished from that of lymphocytic choriomeningitis by a slightly different clinical picture in mice and by immunological studies

4 *Foci of infection near the meninges* Bacterial infections external to the meninges (cervical adenitis, sinusitis, otitis media, mastoiditis, petrositis, epidural abscess, and venous sinus thrombosis) occasionally produce meningeal irritation without the development of purulent meningitis (115) Fever, headache, nausea, vomiting, and stiff neck develop In the cerebrospinal fluid of such cases there is a moderate pleocytosis, and 50 per cent or more of the cells are usually polymorphonuclear leukocytes The sugar content is normal, and no bacteria are present in the fluid The diagnosis is made by the recognition of the focal infection A brain abscess may produce the same clinical picture and spinal fluid findings as an infection external to the meninges A spinal fluid pressure above 400 mm of cerebrospinal fluid with a small reservoir suggests brain abscess

5 *Head injury* Trauma of moderate severity may occasionally be followed by meningitis with a lymphocytic response in the cerebrospinal fluid (116). The following case history illustrates the sudden onset and brief course of such a meningeal reaction.

*Case history*¹² A H, a 13-year-old white schoolboy, entered the Haynes Memorial Hospital, Boston, Mass., on March 11, 1941, with the complaints of headache, vomiting, and stiff neck of 2 days' duration. During the previous month he had enjoyed excellent health. Two days before admission, while he was skiing, he fell forward and struck the right temporal region of his head. He felt dizzy following this accident but he did not lose consciousness. Frontal, bilateral headache soon developed and persisted throughout the night. On the following morning he became nauseated and vomited. He developed stiff neck and a fever of 102°F. On admission to the hospital he was alert, well-oriented, and did not appear ill. The only positive physical findings were a fever of 103°F, a swollen area on his head, stiff neck, and a positive Kernig's sign.

Lumbar puncture revealed ground-glass fluid under an initial pressure of 205 mm of cerebrospinal fluid. There were 870 white blood cells per cu mm, of which 75 per cent were lymphocytes and 25 per cent were large mononuclear cells. The protein content was 50 mgs per 100 cc, and the sugar content was 117 mgs per 100 cc. The white blood cell count was 5,350 with a normal differential. The sedimentation rate was 8 mm per hour, and blood cultures were negative.

Shortly after admission the patient's headache and vomiting ceased. His temperature slowly fell to normal during the first week of illness, while his pulse rate varied from 60 to 85 per minute. After a brief illness he recovered completely.

An attempt to isolate the virus of lymphocytic choriomeningitis from the patient's spinal fluid and blood failed. No complement-fixing or neutralizing antibodies against this virus were demonstrated in his serum after recovery. Although non-paralytic poliomyelitis, mumps meningitis, and other infections cannot be completely excluded, the meningeal reaction in this patient and in similar cases is probably the result of trauma.

6 *Infectious mononucleosis* Occasionally infectious mononucleosis produces a meningeal reaction with a lymphocytic response in the cerebrospinal fluid (117, 118, 119). This picture simulates the meningeal phase of lymphocytic choriomeningitis. However, as the illness progresses, lymphadenopathy, splenomegaly, lymphocytosis, and finally sheep cell agglutinins develop, and the diagnosis of infectious mononucleosis is established. The following case history illustrates the difficulty in early diagnosis.

*Case history*¹¹ V M, a 22-year-old student nurse, was admitted to the Metropolitan State Hospital, Waltham, Mass., on May 19, 1941, with the chief complaints of headache and fever of 2 days' duration. No precursory respiratory or intestinal symptoms preceded her illness, which began suddenly with headache, fever, and generalized aches. These symptoms increased during the next 2 days. On admission to the hospital her temperature was 102°F, and her pulse was 148 per minute. The positive physical findings were mild photophobia, slightly stiff neck, and several 2 cm lymph nodes in each posterior cervical triangle.

Cerebrospinal fluid drawn on May 22 revealed clear fluid under normal pressure, with 12 lymphocytes per cu mm, 17.3 mgs per cent protein, and 85 mgs per cent sugar. The white

¹² The authors were allowed to study this patient through the courtesy of Dr. Conrad Wesselhoef, physician-in-chief, Haynes Memorial Hospital.

¹¹ The authors were able to study this patient through the courtesy of Dr. H. Houston Merritt and of Dr. William Corwin, Metropolitan State Hospital.

blood cell count on May 19 showed 9,800 cells per cu mm, with 84 per cent polymorphonuclear cells, 11 per cent lymphocytes, and 5 per cent transitional cells. Daily blood counts showed an increasing number of lymphocytes, which rose to 78 per cent on June 4. These cells were consistent with those of infectious mononucleosis. Heterophile agglutinins in a titer of 1:256 developed in her serum by May 29.

During the first 2 weeks the patient ran a febrile course with almost daily swings of temperature from 98° to 104°F. Shortly thereafter the temperature returned to normal. Moderate headache and stiff neck persisted during the first week. Small axillary and inguinal lymph nodes developed, the cervical lymph nodes increased in size, and the spleen became palpable during the second week. On June 10 the patient got out of bed, and she was discharged one week later. She has remained well.

7 *Other diseases producing a lymphocytic reaction in the spinal fluid* A number of other infectious diseases may rarely be considered in the differential diagnosis of lymphocytic choriomeningitis. Of the bacterial diseases, brucella and listeria meningitis have been reported. In addition, spirochetal infections (leptospirosis and trypanosomiasis), yeasts (torula), actinomycosis, blastomycosis, rickettsiae (typhus fever), worms (ascaris), and foreign protein injections may produce meningeal symptoms with a mononuclear response in the spinal fluid. A similar meningitis has been reported in leukemia, Hodgkin's disease, and pemphigus. Acute multiple sclerosis may produce the clinical picture of encephalitis with a lymphocytic reaction in the spinal fluid. Rare instances of brain tumor with no localized signs, but with a lymphocytic reaction in the cerebrospinal fluid, do occur. Thus the differential diagnosis includes at least 20 known illnesses. Even if all of these diseases can be excluded, the diagnosis of lymphocytic choriomeningitis can not be made definitely, for the remaining group of cases includes patients with acute aseptic meningitis of completely unknown etiology, as well as cases of lymphocytic choriomeningitis.

8 *Acute aseptic meningitis of unknown etiology* When the virus of lymphocytic choriomeningitis was first isolated, some clinicians suggested that all cases which fulfilled Wallgren's criteria of acute aseptic meningitis were due to this virus. This assumption proved to be incorrect. In a study of 29 cases of acute aseptic meningitis, Baird and Rivers (31) found that only 8 cases (28 per cent) were due to this virus. Armstrong (37) studied the convalescent sera of 53 patients with acute aseptic meningitis and found that in only 32 per cent was there serological evidence of an infection with the virus.

The diagnosis of lymphocytic choriomeningitis is an etiological one based upon the demonstration of virus in the patient's spinal fluid or of the development of antibodies in his convalescent serum. Nevertheless, with a knowledge of the clinical and epidemiological peculiarities of this infection, it is possible in some patients to differentiate cases of acute aseptic meningitis caused by the virus of lymphocytic choriomeningitis from those of unknown etiology. The authors have studied a group of cases of acute aseptic meningitis at the Boston City Hospital and the Peter Bent Brigham Hospital, Boston, Mass. They have been able to predict in some instances whether a particular case was the result of an infection with the virus of lymphocytic choriomeningitis or not. Predictions of virus etiology were made on the bases of the following three criteria:

(a) *Mouse contact* A history of handling dead mice or an observation to suggest contact with mice excreta was obtained. Obviously, this is only circumstantial evidence, for mouse inhabitation does not necessarily mean that the mice are carriers of the virus. In one case the history of handling a dog sick with distemper was obtained.

(b) *The presence of a definite prodromal illness* A febrile systemic infection has been reported in three-fourths of the cases of virus etiology. In contrast with this, in most of the cases of acute aseptic meningitis of unknown etiology, there has been a sudden onset of meningitis with no antecedent prodromata.

(c) *The number of lymphocytes in the cerebrospinal fluid* Rivers studied the maximum cell count in 23 cases of lymphocytic choriomeningitis and in 19 cases of acute aseptic meningitis of unknown etiology. The cell counts in the cases of virus etiology tended to be higher than those in the other group. Of the cases infected with the virus, 48 per cent had more than 1200 cells per cu mm at some time during the meningeal phase, while none in the other group had cell counts that high. When the cell count rises above 600 lymphocytes per cu mm, choriomeningitis virus infection is probable.

The following 3 cases are examples of the diagnostic possibilities of these criteria. In the first 2 cases correct predictions were made, whereas in the third case an incorrect diagnosis was made.

Case 1 A. A. (Boston City Hospital No. 966633), a 23-year-old white, single girl, employed in a clothing factory, was admitted to the hospital on December 31, 1939, with the chief complaint of headache of 5 days' duration.

1) *Mouse contact* The patient's home was not inhabited by mice, but the clothing factory where she was employed to sew buttons on material, was overrun with them. They left their tracks in the button boxes. She had noted that sandwiches left on the work bench for an hour or two were contaminated with their feces.

2) *Precursory symptoms* Nine days before admission, the patient noted the sudden onset of "grippe," characterized by generalized aches, pain in the back, and slight sore throat. Her temperature was 100°F (orally). Shortly afterwards the symptoms regressed and she felt well. Five days before admission she developed headache, dizzy spells, occasional blurring of vision, and stiff neck.

3) *Spinal fluid* The maximum cerebrospinal fluid cell count was 714 lymphocytes per cu mm.

Since this patient fulfilled all 3 criteria, a prediction of lymphocytic choriomeningitis was made, and it was confirmed. Serum drawn in March, 1941, contained neutralizing antibodies against the virus of lymphocytic choriomeningitis.

Case 2 T. B. (Peter Bent Brigham Hospital No. 58656), a 15-year-old white, single girl, was admitted to the hospital on December 29, 1940, with the chief complaints of headache, fever, and vomiting of 3 days' duration.

1) *Absence of mouse contact* No history of any mouse inhabitation of her home could be obtained, and there were no dogs in the household.

2) *Absence of prodromata* This patient was well and attended school every day during December. On December 25 she ate a large Christmas dinner and went to the theatre in the evening. On December 26, a severe headache suddenly developed, followed by fever, stiff neck, and vomiting.

3) *Spinal fluid* The maximum cerebrospinal fluid cell count was 155 lymphocytes per cu mm.

It was predicted during the meningeal phase of her illness that this patient had an acute aseptic meningitis of unknown etiology, not due to the virus of lymphocytic choriomeningitis. Her spinal fluid, blood, and urine were inoculated into mice and guinea pigs with negative results. After recovery no complement fixing or neutralizing antibodies against the virus of lymphocytic choriomeningitis developed.

Case 3 A C (P B B H No 59062), a 27-year-old married, silverpressman, was admitted to the hospital on February 15, 1941, with the chief complaints of headache, fever, shaking chills, and stiff neck of 3 days' duration.

1) *Mouse contact* This patient's home and place of work were both infested with mice. Four months before his illness he had touched a recently killed mouse by the tail at his home.

2) *Prodromata* During the month before his illness the patient had felt quite "tired and run down." He had no definite febrile prodromal illness.

3) *Spinal fluid* The maximum cerebrospinal fluid cell count was 384 lymphocytes per cu mm.

With suggestive epidemiological observations, a prediction of lymphocytic choriomeningitis was made. However, no virus was isolated from the patient's spinal fluid, blood, mouth washings, urine or feces. He did not develop antibodies against the virus of lymphocytic choriomeningitis. Mice trapped at his home and place of work were not carrying the virus.

These illustrations suggest that in some cases one can predict correctly whether or not a particular case of acute aseptic meningitis is due to the virus of lymphocytic choriomeningitis. If the clinical picture is classical, if the epidemiological observations are suggestive, and if there are 600 to 1200 lymphocytes per cu mm in the cerebrospinal fluid, a prediction is probably justified. However, a history of infection which does not fulfill all 3 criteria may or may not be due to the virus. In every case the diagnosis can only be established by virus and serological studies.

J Therapy

1 *Symptomatic therapy* During the meningeal phase of the illness, severe headache is sometimes relieved by repeated lumbar punctures. With the development of paralysis in cases of encephalomyelitis, orthopedic measures are indicated.

2 *Specific therapy* Sulfanilamide has been used in several cases with no apparent change in the course of the disease. In one case with 4 recurrences of meningitis, sulfanilamide was used each time with a prompt fall in temperature (26). However, the recurrences suggest that the therapy was of questionable value. No serum treatment has been reported. Findlay and his co-workers (19) have recently reported a proved case of the disease, which developed during a course of sulfapyridine given for a urethritis. Administration of sulfanilamide failed to alter the progress of the choriomeningitis significantly. Rosenthal (120) has presented evidence that in mice inoculated intracerebrally with this virus, prontosil, but not the other sulfonamides, exerts a slight protective and therapeutic action.

K Summary and conclusions

An attempt has been made to present systematically our knowledge of infections with the virus of lymphocytic choriomeningitis, from a review of the literature and from some of our own data

The conception of the clinical picture of this infection has greatly changed. Experimental evidence suggests that an asymptomatic or febrile, grippe-like illness is probably the commonest form of the disease in man. During this stage the virus may be isolated from the blood with regularity. In some patients this systemic illness is followed by a remission and then by the development of a lymphocytic meningitis in which the virus is present only in the spinal fluid. In a few patients, this second phase of the disease may take the form of an encephalomyelitis. Although generally benign, the disease may be fatal or may produce an obliteration of the subarachnoid space with hydrocephalus or cord symptoms.

The virus of lymphocytic choriomeningitis has a small size of about 40 millimicrons. It has quite a wide range of pathogenicity among animals, monkeys, rats, mice and guinea pigs being susceptible. In all these animals it produces a generalized form of infection with involvement of the meninges, which is particularly marked if intracerebral inoculation is used. Mice that acquire the infection *in utero* or in the suckling period become carriers of the virus, which may be found for long periods in the saliva, nasal washings, blood, urine, feces, and semen. Such mice pass the infection on to succeeding generations *in utero*. Dogs and ferrets may have asymptomatic infections also.

Resistance to reinfection develops rapidly in animals after injection of the virus, but antibodies do not appear until long afterwards. Complement fixing antibodies for the soluble antigen and not the virus itself appear about 4 weeks after onset in man and can be detected for several months. Neutralizing antibodies to the virus itself do not appear until 2 to 3 months after onset, but usually persist for several years. It is possible that in a few patients such antibodies may never appear in detectable amounts.

The pathology of choriomeningitis infection in man, and particularly animals, is that of a generalized infection. Lesions present in all species, though varying in degree, are interstitial pneumonia, focal necrosis of the liver, and choriomeningitis. The latter consists of lymphocytic infiltration of the meninges and choroid plexus, with very little perivascular cuffing and necrosis in the substance of the brain. It is this striking contrast between the intensity of the meningeal reaction and the paucity of lesions in the brain substance which characterizes this infection.

Studies by others have proved that a virus reservoir exists in grey mice in close association with human cases of lymphocytic choriomeningitis. The authors have presented studies on a proved case of choriomeningitis infection, in which the exact time of mouse contact was known. The virus was obtained from mice in the home. Epidemiologic evidence was obtained that a focus of infection had been present in that area for at least 8 years, and that the infection was trans-

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Case 3 A C (P B B H No 59062), a 27-year-old married, silverpressman, was admitted to the hospital on February 15, 1941, with the chief complaints of headache, fever, shaking chills, and stiff neck of 3 days' duration.

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tracerebral injection of 0.03 cc of 100 lethal doses of a virus strain (Virus Strain B) isolated from the grey mice captured at the patient's home.

All of the five mice which had received the bacteria-free brain emulsion from the third mouse developed symptoms on the seventh day after inoculation. Two of them died on the eighth day. A third mouse was sacrificed in order to pass the virus to another generation of mice. The fourth and fifth mice developed severe convulsions but recovered. Since that time the virus has been transferred serially through 20 passages. Its virulence has increased so that on the fifth passage 0.03 cc of a mouse brain emulsion in a dilution of 1:10,000 upon intracerebral injection into mice was lethal on the eighth day. It has maintained this potency in mice.

The guinea pig which had received a subcutaneous injection of 2 cc of the patient's spinal fluid on November 29, developed a fever on the fifth day which rose to 103.5°F (rectally). He lost weight rapidly and shed his hair noticeably. On the thirteenth day after inoculation he appeared weak and dyspneic and died on the following day. An emulsion of his liver, spleen, kidney and lung was injected subcutaneously into a second guinea pig. This guinea pig also developed fever and died on the twelfth day after inoculation.

A second sample of spinal fluid removed from the patient on December 5 was injected into 4 white mice (0.03 cc each intracerebrally). On the seventh day after inoculation the mice developed photophobia, ruffled hair and mild convulsions but their behavior remained active. None of these mice died. Three weeks later these mice received an intracerebral injection of 0.03 cc of 10 lethal doses of a standard strain of lymphocytic choriomeningitis virus¹². They developed no symptoms and were discarded at the end of two weeks under observation.

Blood. On November 29 5 cc of the patient's blood was injected into a guinea pig (4 cc intraperitoneally and 1 cc subcutaneously). From the fifth day to the eighth day after inoculation the guinea pig's temperature ranged from 104° to 104.2°F (rectally). On the fifteenth day he became restless, dyspneic and he began to lose weight rapidly and died on the twenty-fifth day after inoculation.

Mouth washings. On December 2 the patient gargled 20 cc of bacteriological broth. These mouth washings were passed through a Berkfeld V filter. Three Swiss mice were injected intracerebrally with 0.03 cc of the washings and two mice were injected intraperitoneally with 0.1 cc of the filtered broth. None of these mice developed any symptoms of illness. When the mice were inoculated one month later with potent virus they were all susceptible. Therefore, no evidence of the presence of the virus in the patient's mouth washings was obtained.

¹² This virus strain was originally obtained from Dr. Charles Armstrong, National Institute of Health, Washington, D. C. It was received through the kindness of Dr. LeRoy Fothergill, Department of Bacteriology, Harvard Medical School. In this paper it is designated as Virus Strain C.

mitted from one mouse generation to the next *in utero*. Although there is strong evidence for the mouse-to-man transmission of choriomeningitis infection outside of the laboratory, the exact portal of entry of the virus is unknown. Dogs may possibly be the source of some human infections.

The differential diagnosis of lymphocytic choriomeningitis in its meningeal form involves the elimination of all the other known infections which may cause a lymphocytic reaction in the cerebrospinal fluid. In addition, cerebral trauma, foci of infection near the meninges, and tumors, may occasionally produce a similar picture. When these are eliminated, only one case in three of acute aseptic meningitis will be found to be due to choriomeningitis virus. A story of mouse contact, a prodromal illness, and a spinal fluid lymphocyte count over 600/mm³ have been found useful criteria of infection due to this specific virus. The encephalomyelitic form must be distinguished from poliomyelitis and other types of encephalomyelitis. The systemic form must be distinguished from influenza and other febrile illnesses with leukopenia. An etiologic diagnosis can be made only by the isolation of the virus or demonstration of the development of complement fixing or neutralizing antibodies in response to the infection.

Therapy is purely symptomatic at present.

From this survey, it is evident that the role of choriomeningitis virus in unexplained fevers, virus pneumonias, pleurisy with effusion and polyserositis, deserves much more study. The suggestive evidence that this virus may be implicated in some of the atypical encephalitides should be confirmed or disproved.

L Appendix virus studies by the authors

1 *Isolation of the virus from patient E A (Fig 1) Spinal fluid* Spinal fluid, removed from the patient on November 29, was injected into 5 albino, Swiss mice (0.03 cc each, intracerebrally) and into one guinea pig (2 cc subcutaneously). On the seventh day after inoculation, all the mice were inactive, their hair was ruffled. One mouse died on the eighth day in a convulsion with spastic extension of the hind legs, while a second mouse developed convulsions on the eighth day and was sacrificed. The brains of these 2 mice were removed aseptically, and 0.03 cc of a 10 per cent broth emulsion of the brains was injected intracerebrally into each of 2 Swiss mice. A third mouse developed severe convulsions on the ninth day. He was sacrificed, and a brain emulsion was injected intracerebrally into 5 Swiss mice. The remaining two mice developed photophobia, ruffled hair, inactivity and convulsions lasting from the ninth to the twelfth day, but recovered. One month later, they received an intracerebral injection of 0.03 cc of 100 lethal doses of the patient's virus (Virus Strain E A). From these injections the mice developed no symptoms, and they were discarded two weeks later. Thus they showed definite immunity to the patient's virus.

The two mice which had received the emulsion of the brains of Mice 1 and 2 developed convulsions on the eighth day, but recovered from their illnesses. Three weeks later each of these two mice was shown to be immune to the in-

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The guinea pig which had received a subcutaneous injection of 2 cc of the patient's spinal fluid on November 29 developed a fever on the fifth day which rose to 103.5°F (rectally). He lost weight rapidly and shed his hair noticeably. On the thirteenth day after inoculation he appeared weak and dyspneic and died on the following day. An emulsion of his liver, spleen, kidney and lung was injected subcutaneously into a second guinea pig. This guinea pig also developed fever and died on the twelfth day after inoculation.

A second sample of spinal fluid removed from the patient on December 5 was injected into 4 white mice (0.03 cc each intracerebrally). On the seventh day after inoculation the mice developed photophobia, ruffled hair and mild convulsions but their behavior remained active. None of these mice died. Three weeks later these mice received an intracerebral injection of 0.03 cc of 10 lethal doses of a standard strain of lymphocytic choriomeningitis virus¹². They developed no symptoms and were discarded at the end of two weeks under observation.

Blood. On November 29 5 cc of the patient's blood was injected into a guinea pig (4 cc intraperitoneally and 1 cc subcutaneously). From the fifth day to the eighth day after inoculation the guinea pig's temperature ranged from 104° to 104.2°F (rectally). On the fifteenth day he became restless, dyspneic, and he began to lose weight rapidly and died on the twenty-fifth day after inoculation.

Mouth washings. On December 2 the patient gargled 20 cc of bacteriological broth. These mouth washings were passed through a Berkfield V filter. Three Swiss mice were injected intracerebrally with 0.03 cc of the washings, and two mice were injected intraperitoneally with 0.1 cc of the filtered broth. None of these mice developed any symptoms of illness. When the mice were inoculated one month later with potent virus they were all susceptible. Therefore no evidence of the presence of the virus in the patient's mouth washings was obtained.

¹² This virus strain was originally obtained from Dr. Charles Armstrong, National Institute of Health, Washington, D. C. It was received through the kindness of Dr. LeRoy Forthright, Department of Bacteriology, Harvard Medical School. In this paper it is designated as Virus Strain C.

Summary A summary of the results of animal inoculations with spinal fluid, blood and mouth washings from the patient follows

1 Spinal fluid

A November 29 (the seventh day of meningitis)

(1) 5 mice—0.03 cc intracerebrally

a One mouse died with the clinical picture of the virus infection

b Two mice developed symptoms of the virus disease and their brains transmitted the infection to a second generation of white mice

c Two mice developed symptoms of the virus disease and recovered. They developed strong immunity to the virus infection

(2) 1 guinea pig—2.0 cc subcutaneously

This guinea pig developed a clinical picture consistent with the virus infection. An emulsion of his viscera transmitted the disease to a second guinea pig

B December 5 (the thirteenth day of the meningitis)

(1) 4 mice—0.03 cc intracerebrally

These mice developed the symptoms of the virus infection. They recovered and were shown to be immune to a standard strain of the virus of lymphocytic choriomeningitis

2 Blood—November 29 (the seventh day of the meningitis)

A 1 guinea pig—4.0 cc intraperitoneally and 1.0 cc subcutaneously

This guinea pig died on the twenty-fifth day after inoculation, with a clinical course consistent with the virus infection

3 Mouth Washings—December 2 (the tenth day of the meningitis)

A 3 mice—0.03 cc intracerebrally

2 mice—0.1 cc intraperitoneally

These mice developed no symptoms and possessed no immunity to the virus infection

2 *Evidence that virus strain E A was obtained from the patient's spinal fluid, and not from the injected mice* (1) If the virus were being carried in certain members of the mouse stock, immune mice should have been encountered. This was definitely not the case. Every single mouse which was inoculated with the patient's spinal fluid either 1) died of the virus infection, 2) transmitted the virus to a second generation, or 3) was shown to be immune to the virus upon a second inoculation. In contrast with this, every mouse inoculated with mouth washings was found to be susceptible on reinoculation. Furthermore, mice from the same stock inoculated with spinal fluid, blood, urine, feces and mouth washings from other patients, not suffering from the specific virus of lymphocytic choriomeningitis, were all susceptible to subsequent inoculation with the virus of lymphocytic choriomeningitis. In one immunity test on mice previously injected with negative material, every one of 35 mice died between the sixth and eighth days after inoculation with the virus.

(2) In addition, a stock mouse was sacrificed, and a 10 per cent emulsion of his brain was prepared. This was injected intracerebrally into 4 white mice. None of these mice developed any symptoms, and all the mice died upon inoculation with the virus.

(3) Three stock mice were injected intracerebrally with sterile bacteriological broth. None of these mice developed symptoms in two weeks, and all were susceptible to a subsequent inoculation with the virus.

3 *Isolation of the virus from the grey mice* *Mus musculus* at the patient's home From December 10 to 20 box traps were set in the kitchen and bathroom of the patient's home Four live mice were caught A sterile emulsion of liver, spleen and kidney from the first two mice was injected intracerebrally into 6 white mice No symptoms developed and the mice were later shown to have developed no evidence of immunity A brain emulsion from the third grey mouse was injected intracerebrally into 4 mice These mice developed mild symptoms recovered and were later shown to be immune to 10 lethal doses of the standard strain of the virus (Virus Strain C) A brain emulsion prepared from the fourth grey mouse was also injected intracerebrally into four white mice These mice developed no symptoms and were later shown to be susceptible to inoculation with the virus

On December 17 three live grey mice (an adult male a female and a pregnant female) were trapped in the basement of the apartment where the patient lived An emulsion of the livers spleens and kidneys of these three mice was injected into four white mice (0.03 cc intracerebrally and 0.1 cc intraperitoneally) and into one guinea pig (0.5 cc subcutaneously and 0.5 cc intraperitoneally) On the sixth day after inoculation all four of the mice had ruffled hair they were inactive they were breathing rapidly and they had convulsions On the seventh day two of the mice were sacrificed and their organs rapidly frozen On the ninth day the other two sick mice were sacrificed and a brain emulsion was passed to a second generation of five white mice This emulsion also included a brain from a white mouse sick from an emulsion of the embryos of the pregnant grey mouse mentioned above

The guinea pig developed a temperature of 105.4°F. (rectally) on the fifth day and died on the sixth day The lungs showed gross consolidation and hemorrhagic areas An emulsion of its liver spleen kidney, and lung was passed to a second guinea pig (This emulsion showed a colon bacillus contaminant in dextrose broth with no growth on thioglycollate) The second guinea pig developed a fever of 104.5°F (rectally) on the third day and died on the seventh day The lungs showed gross consolidation The heart's blood was sterile on culture

Three embryos from the pregnant mouse caught in the basement of the apartment were removed with great care so that no maternal blood or tissue would contaminate them These were emulsified and injected into three white mice (0.3 cc intracerebrally and 0.1 cc intraperitoneally) On the sixth day after inoculation all three of the mice showed ruffled hair labored breathing and convulsions On the seventh day, one mouse died in a terminal convulsion A second mouse was sacrificed on the seventh day His chest cavity showed bilateral pleural effusions A smear of this fluid showed a predominance of mononuclear cells and no organisms Cultures of the fluid were negative A third mouse was sacrificed on the ninth day and half of his brain was emulsified with the two brains from mice injected with the organ emulsion of the three grey mice trapped in the basement of the apartment building

This brain emulsion deriving from the organs of three grey mice and from the embryos of the pregnant grey mouse was injected intracerebrally into five

white mice in two dilutions. Three mice received a 1:10 dilution and two mice received a 1:1000 dilution of the emulsion. All five mice showed convulsions on the sixth day. One of the mice injected with a 1:1000 dilution died with extension of the hind legs on the sixth day.¹³ The other mouse, which had received the 1:1000 dilution of the emulsion, was sacrificed *in extremis* on the eighth day in order to pass the virus strain. Of the three mice which had received the 1:10 dilution, one was sacrificed and the brain frozen. The other two mice recovered and were later shown to be immune to inoculation with the standard virus strain C.

On the next passage of the grey mouse virus strain (Virus Strain B), the virus was fatal to mice on the eighth day in a dilution of 1:10,000. After its isolation, virus strain B was passed through eleven generations of white mice, until its serological identity with the patient's Virus E A and the standard virus strain C had been definitely established.

Summary. A summary of the results of animal inoculations with emulsions of tissues from grey mice trapped in the patient's home, follows:

- 1 Liver, spleen, and kidney of 3 grey mice—virus infected
 - A 4 white mice—0.03 cc intracerebrally and 0.1 cc intraperitoneally
All 4 mice developed virus infection. Two mice transmitted the virus.
 - B 1 guinea pig—0.5 cc subcutaneously and 0.5 cc intraperitoneally
Fever and death in 6 days. An organ emulsion killed a second guinea pig in 7 days.
- 2 Three embryos of a pregnant, grey mouse—virus infected
 - A 3 white mice—0.03 cc intracerebrally and 0.1 cc intraperitoneally
One mouse died on the seventh day. A second mouse showed bilateral pleural effusions (with mononuclear cells, with no bacteria, and with sterile cultures of the fluid). The third mouse transmitted the virus.
- 3 Brain of one grey mouse—virus infected
 - A 4 white mice—0.03 cc intracerebrally
All mice developed a mild infection, recovered, and were later shown to be immune to the virus.
- 4 Brain of one grey mouse—not infected
 - A 4 white mice—0.03 cc intracerebrally
No evidence of infection, and no immunity.
- 5 Liver, spleen, and kidney of 2 grey mice—not infected
 - A 6 white mice—0.03 cc intracerebrally
No evidence of infection, and no immunity.

4. *Evidence that Virus Strain B was obtained from the grey mice at the patient's home, and not from the injected white mice.* The evidence presented here is similar to that previously presented to show that the Virus Strain E A was isolated from the patient's spinal fluid.

¹³ The apparently greater pathogenicity of the more dilute emulsion appears paradoxical. However, this phenomenon has been described previously with this virus. The following observation was made on the inoculation of chick embryo tissue into white mice: "In a few cases, there seemed to be a 'pre-zone' in the activity of the virus, some of the animals receiving the 1×10^{-1} dilution failing to develop as definite symptoms or even surviving the inoculation, while those in the 1×10^{-2} dilutions reacted characteristically."—Bengston and Wooley (54).

(1) In the course of injections of grey mouse emulsions into white mice, immune and sick white mice were not encountered in a fortuitous manner. Ten white mice were injected with negative emulsions from grey mice. All ten of these mice were later shown to be susceptible to inoculation with the virus. In contrast with this, eleven white mice were injected with grey mouse tissue, from which the virus strain B was isolated. All eleven of these mice showed evidence of the virus infection in one of the following manners: a) clinical picture of the disease, b) death from the virus infection, c) transmission of the virus to a second generation, or d) complete immunity to the virus on a second inoculation. In addition, negative materials, injected into other stock mice at the same time, never resulted in any immunity to the virus.

(2) The presence of pleural effusion in white mice as a result of inoculation with virus-infected grey mouse material is a characteristic response, reported under the same conditions by Armstrong.¹⁴ This fact presents additional evidence that the virus strain existed in a viscerotropic form in grey mouse carriers at the home of the patient.

(3) A brain emulsion of a stock mouse was injected into white mice. It produced no illness and no immunity. Similarly, the injection of sterile broth produced no infection and no immunity in stock mice.¹⁵

Conclusion This evidence definitely shows that virus strain B was isolated from the grey mice at the patient's home and that it was not a virus being carried in the stock mice. Of the six emulsions of grey mouse tissue, three of them showed evidence of virus infection. Approximately 50 per cent of the mice at the patient's home were probably carrying the virus strain B. Thus, when the patient took a dead mouse from a trap at her home just before her illness, there was approximately a 50 per cent chance that her hands came in contact with a mouse carrier of a virus similar to the one which produced her illness. It was next necessary to show that the virus isolated from the patient's spinal fluid and the virus isolated from the grey mice at her home were serologically identical with each other and also with a standard strain of lymphocytic choriomeningitis.

5 Identification of Virus Strains E, A, and B with the standard Virus Strain C of lymphocytic choriomeningitis The evidence presented below demonstrated that the three strains of the virus of lymphocytic choriomeningitis were serologically identical.

A A number of mice, which had received intracerebral injections of one strain of the virus in the course of its isolation, developed typical symptoms and recovered. The immunity of such mice to intracerebral injections of a potent emulsion of a different strain of the virus indicated that the strains were serologi-

¹⁴ When freshly isolated mouse strains are inoculated subcutaneously or intraperitoneally, the animals develop marked difficulty of respiration, and at autopsy the chest cavity is found filled with a clear virus-containing fluid. Lesions are entirely lacking when the neurotropic brain transfer virus is similarly inoculated" (16).

¹⁵ The mice used in these studies were obtained from two sources: (1) Stock mice at the Peter Bent Brigham Hospital, and (2) mice bought from a single breeder of mice. Both sources of mice were tested for possible virus carriers and were found to be negative.

cally identical All of these tests of immunity have been described in the detailed exposition of the isolation of the two virus strains They are summarized in Table 7 In brief, all the mice injected with one strain and then with a second strain were found to be immune, whereas all the controls inoculated for the first time were found to be susceptible

B The serological identity of these three strains was further demonstrated as follows An initial immunizing, subcutaneous dose of one virus was followed

TABLE 7

The results of reinoculation of mice with a different strain of virus following a previous intracerebral inoculation

ORIGINAL INTRACEREBRAL INOCULATION WITH	RE-INOCULATION INTRACEREBRALLY WITH	NUMBER OF MICE INJECTED	NUMBER OF MICE SURVIVING
Virus E A	Virus C	4	4
Virus B	Virus C	7	7
Controls	Virus C	4	1*
Virus E A	Virus B	2	2
Virus C	Virus B	1	1
Controls	Virus B	4	0

* This mouse showed symptoms of the disease, but recovered

TABLE 8

The results of intracerebral inoculations of different virus strains following a previous subcutaneous inoculation

ORIGINAL SUBCUTANEOUS INOCULATION WITH	RE INOCULATION INTRACEREBRALLY WITH	NUMBER OF MICE INJECTED	NUMBER OF MICE SURVIVING
Virus B	Virus E A	4	4
Virus C	Virus E A	4	4
Controls	Virus E A	8	0
Normal brain	Virus E A	4	0
Virus E A	Virus B	4	4
Virus C	Virus B	4	4
Controls	Virus B	4	0
Virus E A	Virus C	3	3
Virus B	Virus C	5	5
Controls	Virus C	4	1

seven days later by an intracerebral injection of 10-100 lethal doses of a different virus strain For example, four mice were injected subcutaneously with 1.0 cc of virus strain E A Seven days later these mice received an intracerebral injection of 0.3 cc of a 1:100 dilution (100 MLD) of virus strain B None of these developed any symptoms, and they were discarded on the fourteenth day At the same time, four mice which had had no previous injection, were inoculated intracerebrally with 0.03 cc of a 1:100 dilution of virus strain B, to act as controls All four of these mice died of the disease in 7 or 8 days As a further control of this method, it was shown that the injection subcutaneously into mice of an emulsion of normal mouse brain induced no evidence of protection

The results of these inoculations are summarized in Table 8, which shows the serological identity of these strains of the virus

C The patient developed in her blood serum specific antibodies, which protected mice against infection with all three strains of the virus. The results of these protection tests are summarized in Table 9. If it is a reasonable assumption that the patient suffered from an infection with only one strain of the virus of lymphocytic choriomeningitis then the development of circulating antibodies to three virus strain certainly suggests their serological identity.

Summary From the three methods of study described, it was evident that the virus strain E A (from the patient's spinal fluid) and the virus strain B (from the grey mice at her home) were serologically identical with or at least very similar to the standard virus strain C.

TABLE 9*

The development of mouse-protective antibodies in the serum of patient E A against three strains of lymphocytic choriomeningitis virus

SERA OF E. A. DRAWN ON	VIRUS DILUTION IN SERUM VIRUS MIXTURE	NUMBER OF MICE SURVIVING		
		E A strain of virus	B strain of virus	C strain of virus
11-30-40	10 ⁻¹	0	1†	1†
	10 ⁻²	0	1†	2†
	10 ⁻³	0	1†	3†
2-3-41	10 ⁻¹	3	3	3
	10 ⁻²	3	3	3
	10 ⁻³	3	3	3

* Dilutions of the virus (1 part) were mixed with the serum (2 parts) and incubated for 4 hours at 37°C. Then 0.03 cc. of each virus-serum mixture was inoculated intracerebrally into each of three white mice. This method was described by Armstrong and Dickens (47).

† These mice all had symptoms of the disease but did not succumb to the infection. It was later found that during 4 hours of incubation at 37°C. virus strains B and particularly C diminished in virulence.

6 *The development of complement fixing antibodies* Serological evidence that the patient E A had had lymphocytic choriomeningitis was obtained by the demonstration of the development of complement fixing antibodies in her serum. Serum removed from the patient on December 19 gave a negative result but serum drawn December 23 was positive when tested for the presence of complement fixing antibodies.¹⁵ The antigen used in these tests was a specific soluble antigen free of virus.

7 *The development of mouse-protective antibodies* Mouse protective antibodies against this virus did not develop until one month later in the course of convalescence than the complement fixing antibodies.

Table 10 presents a study of mouse protection tests on three sera, removed from the patient on November 30, 1940, December 20, 1940, and February 3, 1941. These results were previously summarized in Table 9.

¹⁵ These sera were sent to Dr. L. T. Webster, Rockefeller Institute for Medical Research, New York City, who tested the sera for the presence of complement fixing antibodies.

Summary The development of complement fixing and antiviral antibodies in the patient's serum further verified the fact that she had suffered and recovered from a specific virus infection. The temporal sequence of appearance of these two, apparently distinct, circulating antibodies was studied. Complement fixing antibodies to a specific soluble antigen appeared one month after the onset of the meningitis, but anti-viral antibodies were not demonstrated until two months after the meningitis.

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TABLE 10

Serum-virus protection test The development of mouse-protective antibodies in the patient E A against the virus isolated from her own spinal fluid

SERA OF E A DRAWN ON	VIRUS DILUTION IN SERUM VIRUS MIXTURE	DAY OF DEATH OF MICE*	NUMBER OF MICE SURVIVING
11-30-40	10 ⁻¹	6, 7, 7	0
	10 ⁻²	6, 6, 7	0
	10 ⁻³	8, 8, 8	0
12-20-40	10 ⁻¹	7, 7, 7	0
	10 ⁻²	6, 8	1
	10 ⁻³		3
2-3-41	10 ⁻¹		3
	10 ⁻²		3
	10 ⁻³		3

* The day of death of the mice is an index whether or not they actually died of lymphocytic choriomeningitis. Mice dying from bacterial infections introduced into the brain usually succumb in 2 to 4 days after inoculation. However, mice dying from the sixth to the tenth day with characteristic convulsions are assumed to have died of lymphocytic choriomeningitis. All cultures of injected virus materials were negative.

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TONSILLECTOMY¹ AND POLIOMYELITIS

I EPIDEMIOLOGIC CONSIDERATIONS

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Poliomyelitis is an example of widespread infection but limited disease. Evidence of the general dissemination of the virus is seen clinically in the unbroken gradation from frank paralytic cases, through milder and non-paralytic to suspected abortive forms of the disease. Epidemiologically, the wide dispersion of recognized cases and such features of the disease as its age distribution have long suggested that there are intervening milder forms of the infection or healthy carriers. Extensive development of virus neutralizing antibodies in those with no history of an attack attests widespread distribution of the virus. And, finally, corroboration of this indirect evidence is found in actual detection of the virus.

Formerly, the disease was diagnosed only upon the appearance of its more obvious manifestation, paralysis. Milder degrees of this complication are now detected, and the diagnosis of non-paralytic forms of the disease, with meningeal involvement and increase in cells in the spinal fluid, has now reached proportions equal to the frank clinical disease and an unknown proportion of febrile episodes occurring in close proximity in time and space to clinically recognizable cases indicates perhaps an even more wide-spread occurrence of abortive cases.

From the epidemiologic standpoint, the geographic prevalence (1) and the age distribution of poliomyelitis both bespeak widespread dissemination of the virus. Perhaps largely because of the impressiveness of a few of the larger outbreaks which became the matter of extensive study—such as those of Vermont 1894, Sweden 1905, Massachusetts 1907–1908, New York 1916—and the obscurity, in the earlier years of study, of the relatively small endemic occurrence of the disease in general, poliomyelitis was thought in even comparatively recent times to be regional. But the data which have accumulated concerning the geographic distribution of the disease go far towards removing poliomyelitis from that category of diseases which are due to extraneous local or regional circumstances and tend to give it a place among those diseases which find facilities for transmission in the ordinary associations of man with his fellows—a group of diseases which in general, doubtless because man is rarely out of communication with his fellows, tend toward universality, even though they may be manifest in clinical form in but few of the many exposed to the virus.

¹ In this paper, unless otherwise specified, "Tonsillectomy" refers to the removal of either tonsils or adenoids, or both.

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The age distribution of poliomyelitis (2, 3, 4) conforms to that of well-nigh universal diseases occurring for the most part early in life, and relatively earlier in denser than in more sparsely populated areas. It is thus placed in the group of childhood diseases which in reality are such only in that the chances of infection come earlier in life, immunity resulting from infection accounting largely for the diminution of the disease as older ages are reached.

The neutralization test for immunity has clearly established the fact that antibodies are the result of infection with the virus. These tests, performed in numerous localities, on adults, on individuals at different ages, in urban and rural populations, and in mothers and the newborn, all afford evidence of population immunity corresponding closely to that in other common infectious diseases of childhood (5, 6, 7).

Finally, the finding of the virus (8, 9, 10), not only in frank cases of the disease but in abortive cases and healthy persons as well, lately greatly enhanced by the procedure for its detection in feces (11), is now rapidly corroborating by actual test the concept of widespread dissemination which hitherto had been based more largely on circumstantial epidemiologic evidence.

Due to the distressing nature of this paralytic disease of childhood, the uncertainty as to where it will strike, and its unexpected epidemic tendencies, poliomyelitis has been studied far more exhaustively than many other common infectious diseases to which we have become more accustomed. But in spite of the variety of findings which have been accumulated, there is confusion when an attempt is made to formulate a generally acceptable concept of its behavior. This is due in considerable part to the retention, along with significant findings, of more or less tenuous and irrelevant observations. The inability to discriminate between the significant and the insignificant observations has to some extent been the result of the absence of any one convincing basic demonstration which would set the trend in thought and investigation along more harmonious lines. The sparse distribution of the disease and the limitations in experimental technique have often restricted observations to series too small for analysis as to frequency and reliability, making more difficult the acceptance or rejection of individual investigations. The result has been a habit of generalizing from single observations, seemingly in the direction of some hypothesis which matches the occurrence of the clinical disease in oddity, or which holds some tangible hope of prevention.

With these considerations in mind, it is possible to distinguish a number of epidemiologic features of the disease, not so much because of their numerical frequency, but because of their consistency one with another, which come together into a more satisfactory concept of the disease than can be obtained through any attempt to evaluate single observations each on its own account. Studies of the distribution of the paralytic disease, in the light of the concept of much more widespread dissemination of the virus, afford indications that the occurrence of the frank disease among those exposed to the virus is not only greatly limited but exhibits selectivities which indicate that some added circumstance enters into the determination of whether clinical or subclinical disease results.

upon exposure to the virus. Certain of these selectivities indicate that this added circumstance resides not so much in parasitic factors or in environmental conditions affecting exposure, but in factors of autarcesis³ in the host.

A tendency to familial occurrence (12-13) indicates that susceptibility may be inherent, seasonal and climatic variations (1) in the frequency with which exposure to the virus results in the paralytic disease point to a physiologic function rather than to a fixed anatomic character, the association of the paralytic disease with persons of a certain constitutional type (14, 15, 16-17-18) is suggestive of endocrinologic differences; the suspected association of poliomyelitis with pregnancy (13-19), in view of known mucous membrane alterations due to estrogenic changes, suggests that autarceologic susceptibility may reside in part in the economy of estrogenic substance and, finally, the occurrence of bulbar poliomyelitis following tonsillectomy comprises a demonstration that the nasopharyngeal mucosa may be the locus of the added circumstance which determines the outcome of exposure to the virus.

The present paper is a review and analysis of data available in relation to poliomyelitis following tonsillectomy, a selectivity which is important as indicative of the *modus operandi* of autarcesis—an understanding of which might offer hope of bringing under control the one serious consequence of infection with this virus—and which already provides a means of preventing numbers of cases of a distressing and highly fatal form of the disease.

II. BULBAR POLIOMYELITIS FOLLOWING RECENT TONSILLECTOMY

Early observations

For many years cases of poliomyelitis following recent tonsil and adenoid operations have occasionally been recorded among a large number of other preceding circumstances which at various times have been proposed as possible determinants in the occurrence of the disease. For example, Sheppard (20), who made an epidemiologic study of 200 cases of poliomyelitis in Springfield, Mass., in 1910 stated, "My interest was aroused along this line on account of one or two cases that presented a clinical picture of an acute infection involving the upper respiratory passage with some gastro-intestinal disturbances, in which paralysis seems to have been precipitated by tonsillectomy. Since the exact function of the tonsil is still a matter of speculation, I have sought to collect some data as to the possible significance of its presence or absence in cases of acute epidemic poliomyelitis." He mentioned the examination of 11,858 children in Springfield in the spring of 1910 of whom 3,538 were found to have enlarged tonsils and 1,635 adenoid growths. Over 700 were operated on at different hospitals during 1910 and a large additional number by physicians in private practice. Among this number there were two cases to which Sheppard called attention because of the time relationship between tonsillectomy and the onset of poliomyelitis.

³ Autarcesis is resistance in the host, independent of immunity from exposure to the virus (1).

Case 1 Five years old Male Acute febrile onset July 13, 1910 On the morning of July 14 was operated on for tonsils and adenoids, which, though slightly inflamed, were comparatively normal The following night, July 15, paralysis of both legs was noticed On July 4 the child had an attack of vomiting after eating ice cream, which cleared up entirely before the febrile onset of July 13, during and following the febrile attack there was diarrhea, lasting until the 19th of July The question in this case is whether or not the inflammatory reaction of the tonsils was nature's effort to 'throw off the infection, and whether by depriving the child of his tonsils possibly the paralysis was precipitated

This first case was one in which tonsillectomy was evidently performed after the beginning of symptoms, but before paralysis of the spinal type ensued It is included here simply to show Sheppard's process of thought leading to the opinion that the operation might be a factor in determining paralysis

Case 2 Age six American On September 13, 1910, this child was operated on for tonsils and adenoids, and had a sore throat up to the date of his febrile onset, September 25, which was accompanied by aphonia and dysphagia Paralysis of the neck muscles appeared on October 1 The child was exposed directly to another case of acute epidemic poliomyelitis before and after tonsillectomy and adenoidectomy were performed The question in this case is whether or not the infection with poliomyelitis virus was acquired after the operation on the tonsils and adenoids on September 13, and it cannot well be answered

Case 2 is a typical example of bulbar poliomyelitis following tonsillectomy within the specific interval corresponding to the incubation period of the disease, the subject of this paper

Boyd (21), in his study of an epidemic in the southern Connecticut valley in 1912, grouped cases under various headings "interesting from an etiological point of view," such as association with human cases, with sick animals, following insect bites, wounds, etc He recorded in a last group of "cases of interest for other reasons" preceding circumstances as varied as a man who was a bottle washer and was "exposed to continual dampness", the child of a teamster in whose stable pink-eye was occurring in horses, a man found to be covered with pediculi who "may have received the infection from the bites of these parasites", a child who had been in poor health since it was born and had very little resistance, a child with a history of being on a train across the aisle from "a child who was constantly vomiting (a possible poliomyelitis case)", a woman with a history of being bitten on the left cheek by some insect several days before onset Among the cases in Boyd's last group is one of interest in the present connection

Case 3 A W, female, 7 years American Onset July 15, 1912, abortive case Father an artist Other children 9 and 7 years old This was a very interesting case from the fact that it was next door to where there were two fatal cases If there was any contact between these it was very indirect The patient had her tonsils removed some ten days before by a specialist whose son was afflicted with the disease on July 9 This child was very ill and had the typical symptoms of poliomyelitis without the paralysis

Case 3 is illustrative of a point of view which has been encountered in later years, that infection with the virus of poliomyelitis was conveyed to the patient by the surgeon performing the operation

It should be recalled that, at the time the foregoing observations were made,

modern knowledge of the disease was in its infancy. Experimental study was just beginning, made possible by the transmission of poliomyelitis to monkeys only a few months before. In spite of the earlier, and now classic epidemiologic studies of Caverly and Wickman, poliomyelitis was still generally looked upon as a complete mystery and epidemics as a strange visitation. Because of the absence of the kind of evidence usually sought in infectious disease—its occurrence in those associated in some way with the sick—any hypothesis was considered, especially if it had an extraordinary ring. Certainly, there was little room at that time for a commonplace explanation.

As is frequently true of diseases of the locomotor system, stresses, strains, injuries and falls, exposure to heat or cold or dampness, over-exertion, swimming and wading were most in favor as contributing causes. All such occurrences were noted from the most trivial (as slipping on a rug) to the most severe accidents, and those ranging in time from the moment of detection of the illness to as far back as the memory extended. Attention was focused most sharply upon circumstances immediately preceding the illness, and indeed many of these falls noted were the result of the already present but unrecognized disease, rather than preceding circumstances.

It is not surprising then, that surgical injury of the nasopharyngeal mucous membrane, but one of the many preceding circumstances which were being considered as of possible etiologic interest, did not become at this time the subject of more exhaustive study. Nevertheless, Sheppard seemingly intuitively singled out tonsillectomy from the heterogeneous group of wounds, falls, injuries, exposures, over-exertion, etc., when he wrote

It might be reasonable to suggest at this time that tonsil and adenoid tissue (tonsillar ring of Waldeyer) may offer a resistance to microbic invasion. If this is the case, it might seem on a priori grounds injudicious to remove an inflamed tonsil, especially in the presence of an acute epidemic infection characterized in many instances by involvement of the upper respiratory passage. In Springfield, before and after the acute epidemic of poliomyelitis, it is of interest to note that many operations on tonsils and adenoids were performed.

Determination of the incubation period

The recognition of the obvious manifestations of disease—the appearance of its clinical symptoms and its physical signs—is the event which usually must be considered as marking the beginning of disease. But of more importance in establishing sources of infection is a knowledge of the duration of that asymptomatic period of infection which precedes clinical manifestations—the incubation period. For practical purposes, the incubation period may be defined as the time elapsing between infection and some recognizable sign or symptom of the disease which uniformly appears. In many transmissible infections, it has been fairly accurately determined by repeated observation of a definite interval elapsing between exposure to known sources of infection and the onset of disease. If the incubation period of poliomyelitis had been known, the various events preceding the onset of the disease, which at one time or another have been suspected, could at least have been sifted down to those which, from the point of

view of time alone, could logically have been considered as possible determinant factors

In the experimental disease, the incubation period is now well known. In our experience, monkeys inoculated at various times with a number of strains of virus all developed the disease in 4 to 15 days, the greatest number in 5, 6 and 7 days. But where the virus is modified, as for example by mixture with convalescent serum in the performance of the neutralization test, monkeys may develop the disease after longer incubation periods, although as a rule such mixtures do not produce the disease at all. Such prolonged incubation periods

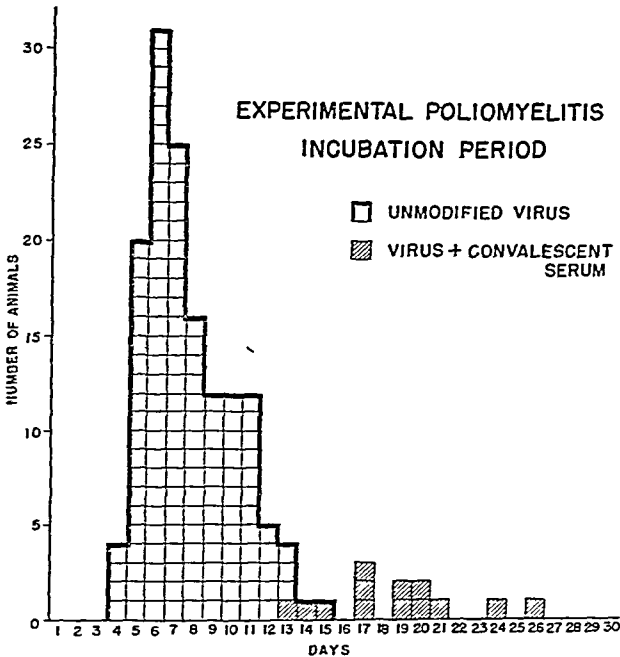


CHART 1 INCUBATION PERIOD OF EXPERIMENTAL POLIOMYELITIS FOLLOWING INTRACEREBRAL INOCULATION WITH UNMODIFIED VIRUS AND MIXTURES OF VIRUS AND CONVALESCENT SERUM

Reprinted from J Prev Med, 3 103, 1929 By W L Aycock and E H Luther

have been interpreted as "partial neutralization" (Chart 1) (22). In carrying out a large number of neutralization tests in various ways, Muckenfuss and Schaeffer (23) observed incubation periods corresponding to that which follows inoculation of unmodified virus when mixtures of normal serum and virus were inoculated into monkeys, while following inoculation of convalescent serum and virus, monkeys developed the disease after distinctly prolonged incubation periods (Chart 2).

Bodian and Howe (24) attempted to estimate the migration velocity of the virus in the sciatic nerve of the rhesus monkey. The method used was inoculation at a single point in the nerve and subsequent cutting at a higher level, at

various intervals in different animals in order to determine how soon after inoculation the nerve must be cut to prevent the virus from passing the point of section and thus infecting the spinal cord. They estimated the latent period to be about 11 hours, and the rate of progression to be approximately 2.4 mm per hour.

If the virus reaches the nervous system along the peripheral nerve with fixed migration velocity it might be expected that the incubation period in man would be longer than in the experimental animal, merely because of the longer anatomical 'distances' in the larger human organism. However, in the experimental disease no clear-cut differences in the incubation period have been established with different routes of inoculation—intracerebral, intranasal, intra-

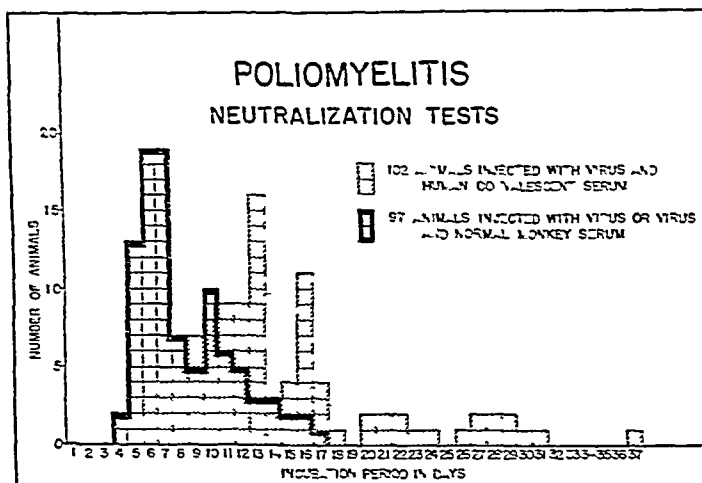


CHART 2 INCUBATION PERIOD OF EXPERIMENTAL POLIOMYELITIS IN ANIMALS INOCULATED WITH MIXTURES OF VIRUS AND NORMAL SERUM, AND VIRUS AND CONVALESCENT SERUM

Reprinted from Experimental Poliomyelitis Natl Fdn for Infantile Paralysis, 1940
By M. Schaeffer and R. S. Muckenfuss

cutaneous, intraperitoneal, etc. Nor does it follow that the incubation period in the experimental disease would necessarily coincide or not coincide with that of the human disease.

In poliomyelitis in man, the majority of cases developed following no known exposure to a source of infection. Inferences were drawn for the most part from the interval between cases in the exceptional instances where there was a history of exposure to the infection. Establishment of the time relationship between associated cases would, it was felt, settle the incubation period, but a suitable situation was not easy to find. Multiple family cases seemed to offer the nearest approach to an epidemiologically related group. Aycock and Eaton (25) therefore re-studied the time interval in 576 multiple cases in 253 families. Abortive cases were excluded from tabulation, since diagnosis is influenced markedly by

proximity to frank cases, their inclusion giving an erroneous impression of the interval between multiple cases

A large proportion (80 per cent) of secondary paralyzed cases were found to occur in the period between the same day as that of the primary case to 8 days following, and the smaller proportion (16 per cent) followed the primary case by 10 to 18 days, averaging 14 days. The first group, it is believed, constitutes common source infections, while those occurring after the longer interval are the true secondary cases. The range of 8 days corresponds to the variation in the incubation period in the experimental disease.

A number of other situations, in which the probable source and time of infection as well as the interval elapsing between exposure and onset can be fixed within more or less definite limits, confirm these conclusions. Milk-borne outbreaks, in which a relatively large number of individuals are infected simultaneously, lend themselves to such studies.

Wickman (26) mentions an outbreak of poliomyelitis in Sweden involving 10 cases in 6 families. The interval between the primary case on a milk farm and 5 secondary cases, all of whom drank the milk, was 14 days.

Dingman (27) reported 8 cases in and about Spring Valley, New York, in 1916. The initial case was on a dairy farm. The 7 secondary cases, persons who consumed raw milk from the farm, became ill 14 to 18 days later. However, from the limited period during which all the cases were in Spring Valley and were consuming the milk in question, the incubation can be set as not under 6 nor over 14 days.

The initial case in a milk-borne outbreak of poliomyelitis in Cortland, New York, in 1925, occurred in a milker on a small dairy farm (28). Subsequently, 8 persons who were supplied milk from this farm developed the disease, 6 cases after an interval of 7 to 12 days, and 2 cases after an interval of 18 days.

An epidemic of poliomyelitis which occurred in Broadstairs, England, in 1926, involving 62 cases, was investigated by Aycock (29). Practically all those stricken were known to be supplied milk from the same dealer. The outbreak started and subsided suddenly, all of the cases being reported within 25 days. However, the time when all the patients were in Broadstairs and were consuming the milk narrows down the period of infection, and it may be inferred that the incubation period in the majority of the cases was 6 to 14 days.

Various other groups of cases studied with a view to setting the incubation period of poliomyelitis (22) have shown it to fall within definite limits. In small, isolated rural areas, cases have been found to occur simultaneously, or separated from one another by an interval of approximately 14 days, even though actual contact could not be traced. The same holds true when there is a history of a single brief contact with a preceding case. For example, in 10 cases developing in 3 related families (30), the period between exposure and onset was 14 days in each case. Within each family, all those attacked became ill on the same day.

The incubation period was not less than 7, nor more than 17 days in 6 cases where contact could be traced. In multiple family cases, where the second case

developed after separation from the first, the intervals fell between 8 and 16 days. In Massachusetts in 1928, where there was history of direct contact with the preceding case, and the exposure was as brief as a single day, the incubation period was not less than 6, nor more than 20 days. When the interval between last exposure and onset was less than 6 days, the duration of exposure was such that the incubation period could have been more than 6 days.

Analogous to the situation in which cases occur following known and limited exposure was the development of 12 cases of paralytic poliomyelitis following injections of poliomyelitis vaccines (31). These individuals all became ill 6 to 14 days following one or the other vaccine injection.

Thus, a large number of observations of different sorts where the point can be established, in both the human and the experimental disease, indicate clearly that the incubation period of poliomyelitis in man is represented by a specific interval of from 7 to 14 days, and is prolonged only in a smaller proportion of cases.

The search for the source of infection, therefore, should be centered at about the fourteenth day before the onset of acute symptoms. With this clearer concept of the incubation period, it becomes possible to distinguish more definitely from among preceding events those circumstances which can be considered as of possible etiologic importance in the occurrence of the disease.

Recent observations

Ayer (32) noted, among observations which seemed to him "impressive as of possible import in the epidemiology of poliomyelitis the occurrence of 9 cases of the bulbar form of the disease 5 to 10 days after tonsillectomy." He has also observed 6 additional cases which he has not reported (33).

The first extended study of poliomyelitis following tonsillectomy in the light of more precise knowledge of the incubation period was made by Aycock and Luther (34). Their data comprised 714 cases of poliomyelitis reported in Massachusetts and Vermont in 1927 and 1928 in which there was information concerning tonsillectomy. They found 36 cases which had had tonsils removed within 1 year of the onset of the disease. Study of the interval in months between operation and attack in this group revealed that of the 36 cases 16 (9 bulbar) occurred within 1 month after the operation, and all of these fell into an interval of from 7 to 18 days (Chart 3), corresponding to the incubation period of the disease, as indicated by multiple family cases, certain contact cases and milk-borne outbreaks, as well as the experimental disease in the monkey.

Five cases of poliomyelitis four of which were bulbar, occurring 9 to 19 days following tonsillectomy, were reported by Silverman (35) in his study of poliomyelitis in Syracuse, New York.

With the foregoing observations in mind, Eley and Flake (36) studied the records of 418 consecutive patients with acute poliomyelitis admitted to the Infants and Children's Hospitals of Boston. There were in this group 287 spinal cases, 7 (2.78 per cent) of whom had had a tonsillectomy within 30 days. Of the 131 bulbar cases, 17 (12.98 per cent) had had tonsils and adenoids excised.

within 30 days prior to illness, and all of these cases fell between 7 and 20 days, in marked contrast to only 3 spinal cases occurring within this period. The interval between operation and onset of both forms of the disease is indicated on Chart 4.

POLIOMYELITIS FOLLOWING TONSILLECTOMY

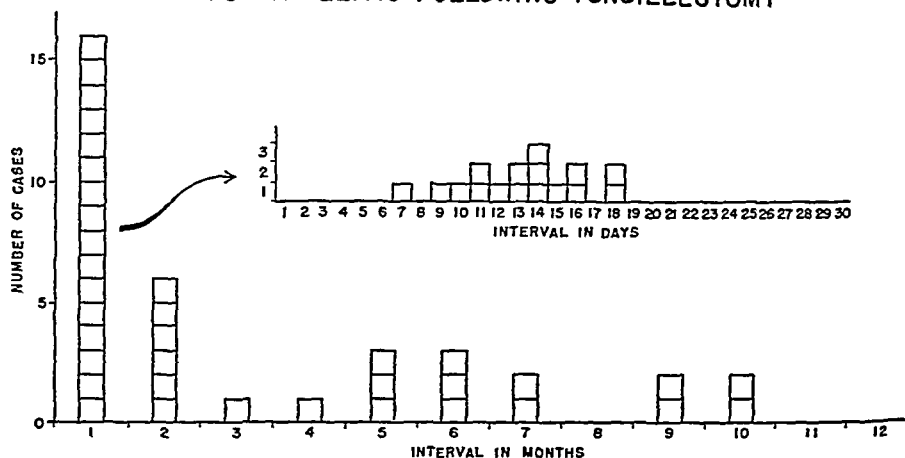


CHART 3 POLIOMYELITIS FOLLOWING TONSILLECTOMY, SHOWING THE INTERVAL IN MONTHS FOR CASES OCCURRING WITHIN A YEAR AND IN DAYS FOR CASES OCCURRING WITHIN ONE MONTH

Reprinted from New England J Med, 200:164, 1929 By W L Aycock and E H Luther

POLIOMYELITIS FOLLOWING TONSILLECTOMY

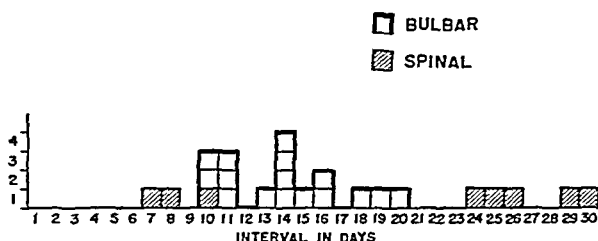


CHART 4 BULBAR AND SPINAL POLIOMYELITIS FOLLOWING TONSILLECTOMY

Reprinted from J Pediat, 13:63, 1938 By R C Eley and C G Flake

An analysis of 686 cases of poliomyelitis in patients who were admitted to the Willard Parker Hospital during 1935 was made by Stillerman and Fischer (37) to determine whether the removal of tonsils in any way influenced the onset or clinical type of the disease. Tonsillectomy had been performed in 10 patients during the month antedating their illness. In 8 of these, poliomyelitis began after an interval of 10 to 12 days, and in the other two, 16 and 22 days, respectively, after the operation. Six of the 10 patients had the bulbar or encephalic

form of the disease. In view of this high incidence, inquiry was made of the 52 patients with poliomyelitis that were admitted to the hospital during the year 1937. Three patients had been tonsillectomized within the month preceding their illness: the disease developed in two in 14 days, and in the third in 21 days. All three had the bulbar type.

The proportion of recently tonsillectomized patients who developed the bulbar or the encephalitic type of poliomyelitis was thus much greater than the incidence of bulbar and encephalitic forms in the complete series. In the 1935 series, 68 of 686 cases, 10 per cent, were bulbar; in the 1937 series, 15 of 52 patients, 28.8 per cent, had bulbar symptoms, while in all 3 patients who had their tonsils removed recently the bulbar type developed.

Fischer, Stillerman and Marks (38) continued their studies on the relationship between tonsillectomy and poliomyelitis during the 1937 epidemic in Toronto. Of the 507 cases included in their data, 231 had had tonsillectomy at some time prior to the onset of the disease, the tonsils of 267 were present, and for 9 there was no information.

Twelve cases of poliomyelitis developed within a month of operation, 7 of which were the bulbar form. Moreover acute poliomyelitis developed more often in those recently tonsillectomized than in others: the increased incidence being due entirely to the excess of bulbar cases. In August, the rate for the total number of cases of poliomyelitis in the recently tonsillectomized group was nearly twice that of the other children; and in September about four times as high. The expected incidence of poliomyelitis both of all forms and of the bulbar form was computed for the recently tonsillectomized children who lived in Toronto. The expectancy for all cases on the basis of actual incidence in other groups of children, was 4.5 and the occurrence was 8. As for bulbar poliomyelitis the computed figure was 0.3 case as compared with 4 cases actually occurring. Consequently, the high incidence of poliomyelitis in the recently tonsillectomized group is accounted for by the excess of cases of the bulbar form of the disease.

The Department of Health of the Province of Ontario (39) reported in the 1937 outbreak 9 cases in which tonsillectomy had been performed within one month prior to onset. Six of these cases developed paralysis: 4 being of the bulbar type. The interval from operation to onset in 4 cases was 7 days, and in the other 5 cases was 10, 14, 21, 24 and 26 days.

Top and Vaughan (40) in their study of the Detroit epidemic of 1939 give certain facts concerning tonsillectomy and poliomyelitis but their data do not permit of tabulation in the present series because information is not given as to the type of the disease or the interval between operation and onset. There was a history of tonsillectomy in 215, or 41.3 per cent of the 521 cases reported while 20 of the 23 fatal cases were patients with a history of tonsillectomy. Because of the higher fatality in bulbar poliomyelitis it is likely that the fatal cases, almost all of which were in tonsillectomized individuals contained a higher proportion of bulbar poliomyelitis than did the non-fatal cases.

From the nature of the case—the relative uncommonness of poliomyelitis

and the numerical infrequency of bulbar cases following tonsillectomy—the figures obtained in any one outbreak or by any one observer are likely to be too small to be generally convincing. All of the cases of poliomyelitis following recent tonsillectomy which have been reported in the literature and which have otherwise come to our knowledge are summarized in Table 1. In some of the series no mention is made of cases occurring more than 30 days after the operation, the longer period presumably not being studied.

TABLE 1

Poliomyelitis following recent tonsillectomy according to clinical type of disease

INTERVAL										TOTAL CASES	REFERENCES
Within 30 days					30 to 60 days						
B	BS	Unkn	S	NP	B	BS	Unkn	S	NP		
1				1						1	Sheppard 1910 (20)
										1	Boyd 1912 (21)
9										9	Ayer 1928 (32)
7	5		4							16	Aycock and Luther 1929 (34)
4		2								6	Gordon 1931 (41)
5										5	Silverman 1931 (35)
4			2	3						9	Ontario Health Dept 1937 (39)
2										2	Anderson 1938 (43)
15	2		4	3	1			3	1	29	Eley and Flake 1938* (36)
6	3		2	2						12	Stillerman and Fischer 1938 (37)
1										1	Pamment 1938 (44)
1				2						3	Kramer and Gilliam 1938 (45)
1										1	Stebbins, Gillick and Ingraham 1939 (46)
2										2	Koskoff 1939* (42)
5	2		2	3	2			13		27	Fischer, Stillerman and Marks 1941 (38)
2	3		1	1						7	Helms 1941 (48)
5										5	Krill and Toomey 1941 (47)
15	5	5	5	3	5		4	11		53	Vt 1912-31, Mass 1927-31
14	2		2	2		1	1	3		25	Personal Communications
99	22	7	22	20	8	1	5	30	1	215	

* Adenoidectomy only on 1 case. Type B—Bulbar B-S—Bulbo-spinal Unkn—Type unknown S—Spinal NP—Non-paralytic

The cases represented in table 1 for which the necessary data were available are plotted on chart 5, according to the type of case and the interval in days between tonsillectomy and onset. It may be seen that in the cases following the operation within 30 days, the bulbar type predominates, while in those occurring between 30 and 60 days later, spinal cases are more frequent.

The four main categories of cases shown in chart 5—those with bulbar involvement within 30 days and in 30-60 days, and those with spinal involvement within 30 days and in 30-60 days—may not be comparable in all respects. Some of the series in this tabulation do not include cases in the 30-60 day period, and

some refer to bulbar poliomyelitis only. Neither can interpretations be made as to frequencies for the reason that the actual total numbers of cases which furnished these figures are not known. Nevertheless, the cases are comparable in general, in so far as the relative numbers of the different types are concerned, and are strictly comparable in respect to the interval in days between the operation and the onset of the disease for the different types.

POLIOMYELITIS FOLLOWING TONSILLECTOMY

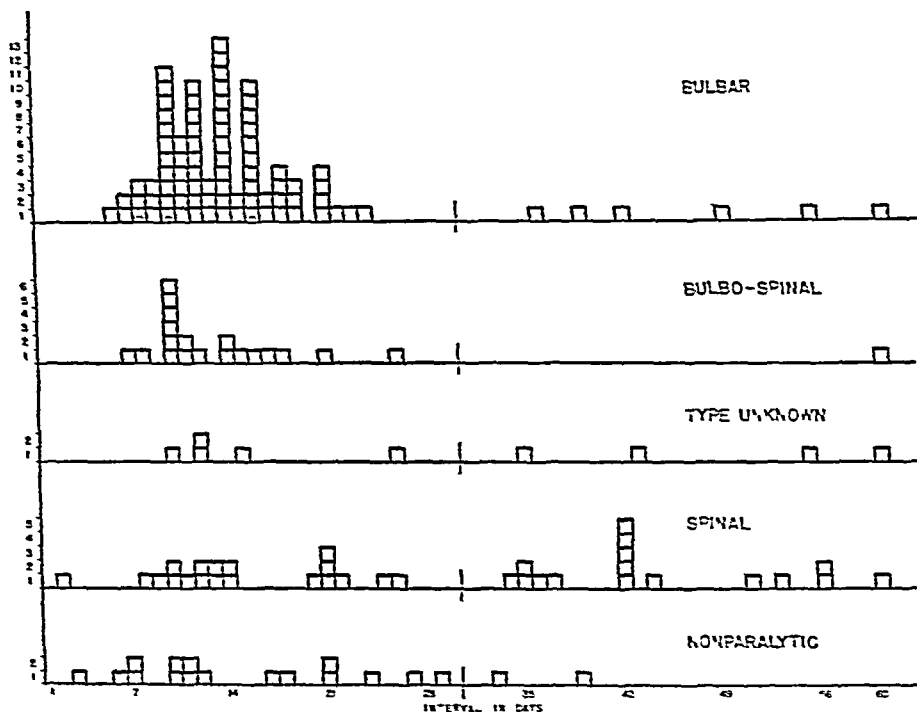


CHART 5 POLIOMYELITIS FOLLOWING RECENT TONSILLECTOMY ACCORDING TO INTERVAL IN DAYS AND CLINICAL TYPE OF DISEASE
(A = adenoidectomy only)

It may be seen that the less common bulbar poliomyelitis predominates over the spinal form about 5 to 1 in the cases occurring within 30 days following tonsillectomy, while in the 30-60 day period spinal cases are in the ascendancy in nearly the same proportion as they exceed bulbar poliomyelitis in general. Furthermore, the concentration of bulbar cases following tonsillectomy in the 30 day group at a specific interval of 7 to 21 days (corresponding to the incubation period of the disease), as compared with the random distribution of bulbar cases in the 30-60 day group and of spinal cases throughout the whole period constitutes a strong indication that the bulbar cases within 30 days are for the most part specifically related to the operative procedure. A small proportion

of the bulbar cases occurring within 30 days, the bulbar cases in the 30-60 day group, and the spinal cases within the whole 60 day period are interpreted as not being specifically associated with the operation

Seasonal occurrence of poliomyelitis following tonsillectomy

The more precipitous seasonal occurrence, not only of bulbar poliomyelitis following tonsillectomy by a specific interval, but of chance cases following the operation, as compared with the seasonal occurrence of the disease in general, is regarded as the result of coincidence of the season of prevalence of poliomyelitis

**POLIOMYELITIS
PERCENTAGE SEASONAL DISTRIBUTION**

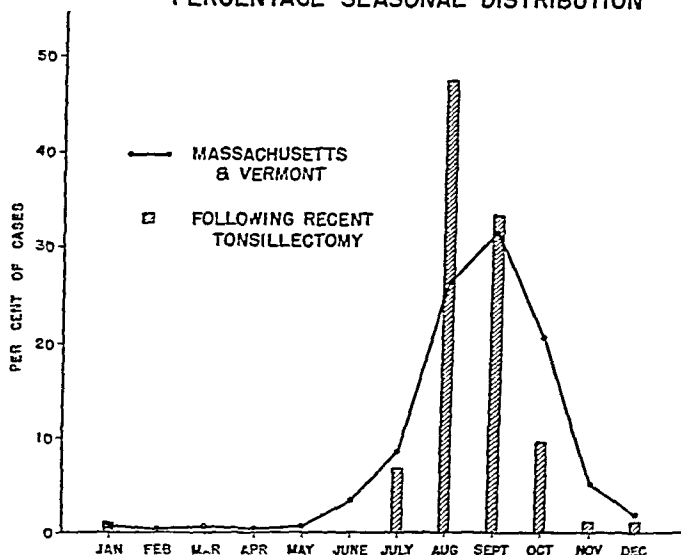


CHART 6 SEASONAL OCCURRENCE OF POLIOMYELITIS FOLLOWING TONSILLECTOMY WITHIN ONE MONTH AS COMPARED WITH SEASONAL PREVALENCE OF POLIOMYELITIS IN GENERAL

with the time of year during which larger numbers of elective operations are done (Chart 6)

Poliomyelitis following adenoidectomy only

Since for the most part the data upon which this analysis is based are not specific as to tonsillectomy or adenoidectomy, but probably in the majority of instances, particularly in the younger age groups, refer to both, it is not clear whether tonsillectomy, adenoidectomy or both are concerned in bulbar poliomyelitis following recent operations. In the series collected, 4 cases followed adenoidectomy only (table 2). This small number could represent chance occurrence, but the intervals correspond to the period observed in the majority of bulbar cases following tonsillectomy.

Operations for the removal of both tonsils and adenoids and of adenoids alone are performed more often in younger children, so that in this age group adenoid-

ectomy might be the determining factor. However, in older individuals the operation does not so often include the removal of adenoids, and it will be noted from the age distribution of bulbar poliomyelitis following tonsillectomy (Chart 7) that many cases fall into the age group comprising individuals who probably had tonsillectomy only.

Poliomyelitis following tooth extractions

Other operative procedures carried out shortly before the onset of poliomyelitis have been noted by a number of observers. In the course of this study, a small number of tooth extractions have come to notice in the literature and have been reported in personal communications (table 3).

TABLE 2
Poliomyelitis following adenoidectomy

INTERVAL	TYPE	AGE	REFERENCE
10 days	Bulbar	7	Eley and Flake (36)
16 days	Bulbar	6	Personal records (Mass.)
8 days	Bulbar	5	Koskoff (42)
7 days	Non-paralytic	8	Fischer, Stillerman and Marks (38)

TABLE 3
Poliomyelitis following tooth extractions

INTERVAL	TYPE	REFERENCE
2 days	Unknown	Personal communication
3 days	Bulbar	Personal communication
3 days	Spinal	Personal communication
3 days	Unknown	Gordon (41)
6 days	Unknown	Gard (49)
10 days	Unknown	Gard (49)
Within 3 months (8 cases)	Unknown	Personal communication
4 months	Unknown	Personal communication

Because but few cases of poliomyelitis follow this more common procedure, because the specific interval corresponding to the incubation period does not appear, and because no particular form of the disease is indicated, the small number of cases so far recorded is not sufficient to bring tooth extraction into consideration as a factor in the occurrence of poliomyelitis. It would appear that this reported circumstance can be relegated to the category of miscellaneous precedent circumstances, such as those discussed in the beginning of this paper, which have at various times been suggested as etiologic factors.

Experimental bulbar poliomyelitis following inoculation into the tonsillar region

There are many reasons for thinking that the experimental disease in the monkey is not an exact counterpart of poliomyelitis in man. This is particularly true of the type of disease occurring naturally and that following experimental

of the bulbar cases occurring within 30 days, the bulbar cases in the 30-60 day group, and the spinal cases within the whole 60 day period are interpreted as not being specifically associated with the operation

Seasonal occurrence of poliomyelitis following tonsillectomy

The more precipitous seasonal occurrence, not only of bulbar poliomyelitis following tonsillectomy by a specific interval, but of chance cases following the operation, as compared with the seasonal occurrence of the disease in general, is regarded as the result of coincidence of the season of prevalence of poliomyelitis

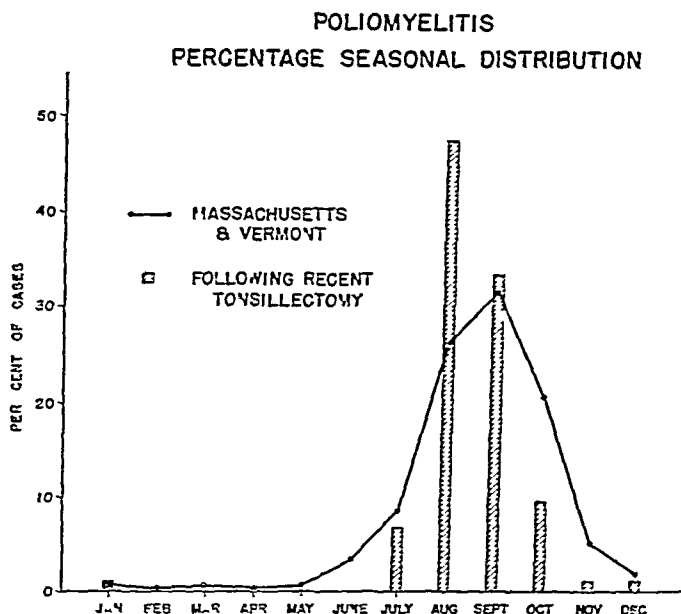


CHART 6 SEASONAL OCCURRENCE OF POLIOMYELITIS FOLLOWING TONSILLECTOMY WITHIN ONE MONTH AS COMPARED WITH SEASONAL PREVALENCE OF POLIOMYELITIS IN GENERAL

with the time of year during which larger numbers of elective operations are done (Chart 6)

Poliomyelitis following adenoidectomy only

Since for the most part the data upon which this analysis is based are not specific as to tonsillectomy or adenoidectomy, but probably in the majority of instances, particularly in the younger age groups refer to both, it is not clear whether tonsillectomy, adenoidectomy or both are concerned in bulbar poliomyelitis following recent operations. In the series collected, 4 cases followed adenoidectomy only (table 2). This small number could represent chance occurrence, but the intervals correspond to the period observed in the majority of bulbar cases following tonsillectomy.

Operations for the removal of both tonsils and adenoids and of adenoids alone are performed more often in younger children, so that in this age group adenoid-

of tonsillectomy, regardless of when performed, was over twice that in the non-tonsillectomized children with the disease, 18.7 and 7.5 per cent, respectively.

In the Report on Poliomyelitis in Ontario (1937) (39), data are given on 144 cases in respect to type of paralysis and history of tonsillectomy. The proportion of bulbar cases was considerably greater where tonsils had been removed: of 54 cases in which tonsils were present, 11 per cent were bulbar, while of 93 cases who have a history of previous tonsillectomy, 35.5 per cent were bulbar.

Top and Vaughan (40), in a report of the Detroit epidemic of 1939, stated that non-tonsillectomized patients developed bulbar paralysis in 4.2 per cent of cases, while patients previously tonsillectomized—whether within one month, one year, or over a year of the onset of poliomyelitis—developed bulbar paralysis in 27 per cent of cases.

Stebbins, Gilick and Ingraham (46) reported an outbreak in Niagara Falls, New York, in 1938, in which bulbar paralysis occurred with unusual frequency, 13 of the 20 patients having involvement of this type. The primary case was a bulbar poliomyelitis following tonsillectomy by 14 days. Only 3 other cases in the group—1 bulbar, 1 spinal, and 1 non-paralytic—had ever had tonsillectomy, and all of these were done at some previous time.

Although the first case in this outbreak followed tonsillectomy, the operation did not appear to be the determining factor in the high proportion of cases with bulbar involvement. It should be stated that, unlike the other series showing higher proportions of bulbar cases in tonsillectomized patients—of which the majority had bulbar involvement only—in the present group, only the single case following tonsillectomy by 14 days was straight bulbar. The other 12 cases (in 11 of whom tonsils had not been removed) were combined bulbar and spinal.

Cases in Massachusetts, 1927-1931

Case records of 918 cases occurring in Massachusetts from 1927-1931, inclusive, on which data were recorded in regard to presence or absence of tonsils and type of paralysis, show that of 210 bulbar cases, 122 or 58.1 per cent were in individuals in whom tonsils had been removed. Of 638 spinal cases, 146, or 22.8 per cent, were in tonsillectomized individuals.

Cases in Vermont, 1912-1931

Similar records in Vermont, covering the period 1912-1931, inclusive, comprised 473 cases with information both as to tonsillectomy history and type of paralysis. Of 54 bulbar cases, 12 or 22.2 per cent gave a history of previous operation, while only 19 or 4.5 per cent of 419 spinal cases were in individuals who had had tonsils removed.

Cases from various localities, 1941

During 1941, we received information concerning clinical types of poliomyelitis in relation to presence or absence of tonsils from 12 widely separated localities in the United States and Canada. Some of these groups comprise cases occur-

inoculation, and it is believed that too sharp inferences from the experimental disease cannot always be drawn with reference to the human disease

Landsteiner, Levaditi and Danulesco (50) produced poliomyelitis in a monkey by submucous injection into the tonsillar area. Levaditi and Danulesco (51) failed to induce the disease by rubbing or painting the tonsils of three monkeys with virus, while application of the same virus to the nasal mucosa was followed by typical poliomyelitis. Such experiments are not particularly indicative, in view of the fact that monkeys develop poliomyelitis with greater or less frequency resulting from numerous routes of inoculation.

Sabin (52) observed that mere transitory contact between the normal or injured pharynx or tonsils of monkeys and the virus of poliomyelitis was not enough to produce the disease, but it was possible to infect these animals when the virus is injected into the tonsillopharyngeal region. Animals inoculated in this manner developed bulbar or bulbo-spinal manifestations with great frequency, as compared with animals inoculated, for example, by intranasal instillation of virus.

It is interesting that Sabin failed to produce poliomyelitis in monkeys by applying the virus immediately to a tonsillectomy wound, while the disease did develop following injection into the tonsillar region. From this finding, he reasoned that it would be expected that, in the human being, bulbar poliomyelitis following tonsillectomy would occur where the virus was already present at the time of the operation, rather than as a result of contamination of the wound afterwards. This is in accord with the indications seen in the occurrence of bulbar poliomyelitis following tonsillectomy at a specific interval corresponding to the incubation period of the disease, as contrasted with what would be expected if the disease were the result of contamination subsequent to the operation.

III PRESENCE OR ABSENCE OF TONSILS IN RELATION TO CLINICAL TYPES OF POLIOMYELITIS

Observations in the literature

The earlier study of Aycock and Luther (34), aside from the finding that bulbar cases followed the operation at a specific interval, did not indicate a relationship in general between poliomyelitis and the presence or absence of tonsils. Information on 714 out of 1,224 cases of poliomyelitis revealed tonsillectomy in 217, or 30 per cent, a percentage in keeping with the estimates for the general population at corresponding ages. However, the comparative frequency of the bulbar and spinal forms of the disease was not studied in relation to presence or absence of tonsils. A number of investigators have subsequently dealt with this point.

Eley and Flake (36) noted that 74 (56.5 per cent) of 131 bulbar cases and 95 (32 per cent) of 297 spinal cases had had tonsils excised at some time more than 30 days previous to the onset of poliomyelitis. Fischer, Stillerman and Marks (38) found in the epidemic of poliomyelitis in Toronto in 1937 that the percentage of cases of the bulbar form among children with poliomyelitis who had a history

groups the trend is in the direction of a relatively higher frequency of bulbar poliomyelitis in individuals with a previous tonsillectomy. The smaller number of non-paralytic cases is more nearly in keeping with combined spinal and bulbar poliomyelitis in respect to previous tonsillectomy.

Discussion

Table 5 is a summary of cases of poliomyelitis with a history of tonsillectomy performed more than 30 days previous to the onset of the disease, which have been collected from the literature, from personal communications, and from our own records.

The fact that non-paralytic poliomyelitis occurs in tonsillectomized and non-tonsillectomized individuals with the same frequency as the bulbar and spinal forms combined (as may be seen in table 5)—that is, conforms to the total cases

TABLE 5
Poliomyelitis according to presence or absence of tonsils and clinical type

BULBAR AND BULBO-SPINAL			SPINAL			NON-PARALYTIC			TOTAL CASES	REFERENCE
Number of cases	Tonsils present	Tonsils removed*	Number of cases	Tonsils present	Tonsils removed*	Number of cases	Tonsils present	Tonsils removed*		
114	40	74	279	184	95				393	Eley and Flake (36)
59	20	39	184	106	78	247	141	106	490	Fischer et al (38)
210	88	122	638	492	146	70	48	22	918	Mass 1927-31
104	43	61	262	184	78	57	35	22	423	Personal Communications
35	6	29	106	48	58				141	Ontario Health Dept (39)
54	42	12	419	400	19				473	Vermont 1912-1931
12	11	1	6	5	1	1	0	1	19	Stebbins et al (46)
588	250	338	1,894	1,419	475	375	224	151	2,857	

* Not including cases with tonsils removed within 30 days of onset

of poliomyelitis in respect to the presence or absence of tonsils—might be taken as an indication that the removal of tonsils is a determinant, not between non-paralytic and paralytic poliomyelitis, but rather between the bulbar and spinal forms of the disease.

To facilitate comparison between the different sets of figures, in table 6 are given percentages of all cases of poliomyelitis with a history of tonsillectomy, percentages of all cases of the bulbar and spinal types, and percentages of these types with a history of tonsillectomy. The percentages of all non-paralytic cases are given where available, and the percentages of these cases which gave a history of tonsillectomy.

In the first four sets of figures, the percentages of total cases giving a history of removal of tonsils are fairly uniform. The proportions of bulbar cases are also uniform, and give a history of tonsillectomy about twice as frequently as do the spinal cases.

ring in the locality during part or all of the 1941 season, others are cases admitted to certain hospitals during the season, and still others represent the cases which

TABLE 4
Polio myelitis according to presence or absence of tonsils and clinical type

LOCALITY*	BULBAR AND BULO-SPINAL			SPINAL			NON-PARALYTIC			TOTAL CASES
	Number of cases	Tonsils present	Tonsils removed†	Number of cases	Tonsils present	Tonsils removed	Number of cases	Tonsils present	Tonsils removed	
1936-37-39 Washington, D C	7	4	3	13	10	3	0	0	0	20
1940 Los Angeles, Cal	5	4	1	3	1	2	7	3	4	15
1941										
Washington, D C	3	2	1	40	26	14	3	1	2	46
Providence, R I	5	0	5	3	1	2	0	0	0	8
Washington Co, Miss	0	0	0	1	1	0	2	2	0	3
Boston, Mass										
Children's Hospital	4	2	2	10	7	3	2	1	1	16
Haynes Memorial	4	1	3	10	5	5†	1	1	0	15
Louisville, Ky	3	2	1	25	21	4	4	2	2	32
Nashville, Tenn	4	2	2	16	15	1	0	0	0	20
Knoxville, Tenn	0	0	0	10	8	2	0	0	0	10
Fredericton, N B	4	3	1	9	8	1	4	3	1	17
Winnipeg, Can	11	2	9	11	7	4	10	8	2	32
Philadelphia, Pa	1	0	1	3	3	0	0	0	0	4
Cleveland, Ohio	53	21	32	108	71	37	24	14	10	185
Total	104	43	61	262	184	78	57	35	22	423

* We are indebted for these data to Dr R H Detweiler, Children's Hospital, Washington, D C, Dr H S Barrett, Charles V Chapin Hospital, Providence, R I, Dr J P Ward, Washington Co Health Dept, Greenville, Miss, Dr C Wesselhoeft, Haynes Memorial Hospital, Boston, Mass, Dr W E Dierking, Louisville City Hospital, Louisville, Ky, Dr W C Williams, State Dept of Health, Nashville, Tenn, Dr W H Enners, Health Officer, Knoxville, Tenn, Dr J M Cameron, District Medical Health Officer, Fredericton, N B, Dr Maxwell Bowman, Epidemiologist, Dept of Health and Public Welfare, Winnipeg, Canada, Dr Thomas Farmer, Pennsylvania Hospital, Philadelphia, Pa, Dr J A Toomey, City Hospital, Cleveland, Ohio, Dr John F Kessel, Los Angeles Co Hospital, California

Since this table was compiled data on 95 cases in Detroit, Mich, which are in accord with these figures, have been received from Dr Franklin H Top

† Not including cases with tonsils removed within 30 days of onset

‡ 1 case had tonsils only removed

were in the hospital at the time of inquiry. Similar data from one hospital for 1936, 1937 and 1939 are included. This information is summarized in table 4.

Though the number of cases in each of the series is small, in 11 out of 12 of the

IV CLINICAL TYPES OF POLIOMYELITIS WITH REFERENCE TO PRESENCE OR ABSENCE OF TONSILS IN FAMILIAL OUTBREAKS

Exclusion of parasitic and environmental variables

When two or more cases of poliomyelitis occur in the same family simultaneously many epidemiologic factors can be assumed to be the same. It is most likely, for example, that these groups of cases are the result of exposure to a single strain of virus. Environmental circumstances, too, such as economic, social and sanitary status, dietary regimen, geographic location and seasonal occurrence may be excluded as operating variants, as well as many host factors which may be invoked, such as race and family. Thus these family outbreaks, as pointed out in the discussion of the incubation period, comprise self-contained groups of cases from which many of the variables which might enter into other groups can be excluded.

The records of 46 families, comprising 103 cases where the desired information was available, are given in table 7, showing the number of families, the type of cases occurring, and whether tonsils were recently or previously removed, or were still present.

Poliomyelitis following recent tonsillectomy

The group developing bulbar poliomyelitis following recent removal of tonsils includes a family with 5 simultaneous cases which occurred within the incubation period of the disease, on all of whom the operation had been done on the same day (47). It should be noted that a sixth child in this family was not tonsillectomized and did not have poliomyelitis.

One family had 3 simultaneous bulbar cases. 2 followed recent removal of tonsils, and 1 followed adenoidectomy only, all performed at the same time.

There were 2 bulbar cases in each of 2 families. In the first family, both children had been recently tonsillectomized, and in the second, the tonsils had not been removed in either patient.

Clinical type of poliomyelitis according to presence or absence of tonsils

In 12 families there were both bulbar and spinal cases. It may be seen that the bulbar type predominated in those individuals who had been recently or previously tonsillectomized, while there were more cases of the spinal type in those with tonsils present.

Finally, in the families with only the spinal type of poliomyelitis, the majority (55 of 62) were in non-tonsillectomized individuals.

As will be seen in the next section, poliomyelitis in general tends to occur at somewhat older ages than the spinal form. It might be suggested, therefore, that the tendency for multiple cases in families to run to the bulbar form in tonsillectomized individuals is in reality a matter of age. However, it is clear from the analysis in the next section that age itself (rather than absence of tonsils) hardly suffices as the explanation for the difference between bulbar and spinal poliomyelitis in tonsillectomized and non-tonsillectomized members of the same family (table 8).

The Ontario figures show a higher percentage of poliomyelitis cases with a history of tonsillectomy than the other series. However, the percentage of bulbar cases in the outbreak was the same, and, likewise, the percentage of bulbar cases giving a history of removal of tonsils was about twice that of the spinal cases. But since the number of cases in which information was available concerning the operation represents only a small proportion of the total number of cases in the outbreak, it is not clear that the higher percentage of cases here with a history of tonsillectomy is not due to the manner of selection of the cases.

The Vermont series, extending from 1912-1931, covers a period when tonsillectomy evidently was not as frequent as in the period covered by the other series. The percentage of poliomyelitis giving a history of removal of tonsils is much smaller, and the percentage of total cases which were bulbar is also

TABLE 6

Poliomyelitis according to presence or absence of tonsils and clinical type

TOTAL CASES	PER CENT TOTAL TONSILS REMOVED*	PARALYTIC CASES				NON-PARALYTIC CASES		REFERENCE
		Bulbar		Spinal		Per cent total	Per cent tonsils removed*	
		Per cent	Per cent tonsils removed*	Per cent	Per cent tonsils removed*			
393	43 0	29 0	64 9	71 0	34 1	50 4	31 4	Eley and Flake (36)
490	45 5	24 3	66 1	75 7	42 4			Fischer et al (38)
918	31 6	24 8	58 1	75 2	22 9	7 6	31 4	Mass 1927-1931
423	38 0	28 4	58 7	71 6	29 8	15 6	38 6	Personal Communications
141	61 7	24 8	82 8	75 2	54 7			Ontario Health Dept (39)
473	6 6	11 4	22 2	88 6	4 5			Vermont 1912-1931
19	15 8	66 7	8 3	33 3	16 7	5 3	100 0	Stebbins et al (46)
2,857	33 8	23 7	57 4	76 3	25 1	13 1	40 2	

* Not including cases with tonsils removed within 30 days of onset

small. But the bulbar cases give a history of tonsillectomy with much greater frequency than the spinal cases.

Thus, six series are consistent in showing that cases of the bulbar type of poliomyelitis give a history of removal of tonsils with much greater frequency than spinal cases of the disease.

The outbreak reported by Stebbins, Gilck and Ingraham (46), at the outset differing from the other series in that a much higher percentage of cases were bulbar, is exceptional in regard to tonsillectomy. Sixty-six per cent of the cases were of the bulbar type, with only 8 per cent giving a history of removal of tonsils. It is clear, therefore, that the absence of tonsils was not the factor which determined such a large percentage of bulbar cases in this outbreak.

No reason is assigned for the high proportions of cases with bulbar involvement. Such explanations as a particular strain of virus with bulbar predilection, differences in mode of spread, or in population susceptibility have been suggested. In outbreaks of this sort, many such variables cannot be excluded.

ABSENCE OF TONSILS AND THE OCCURRENCE OF POLIOMYELITIS WITH REFERENCE TO AGE

In Chart 7 is given the percentage age distribution for bulbar and spinal poliomyelitis, both in individuals with tonsils present and in those with tonsils removed. This graph compiled from case records in Vermont and Massachu-

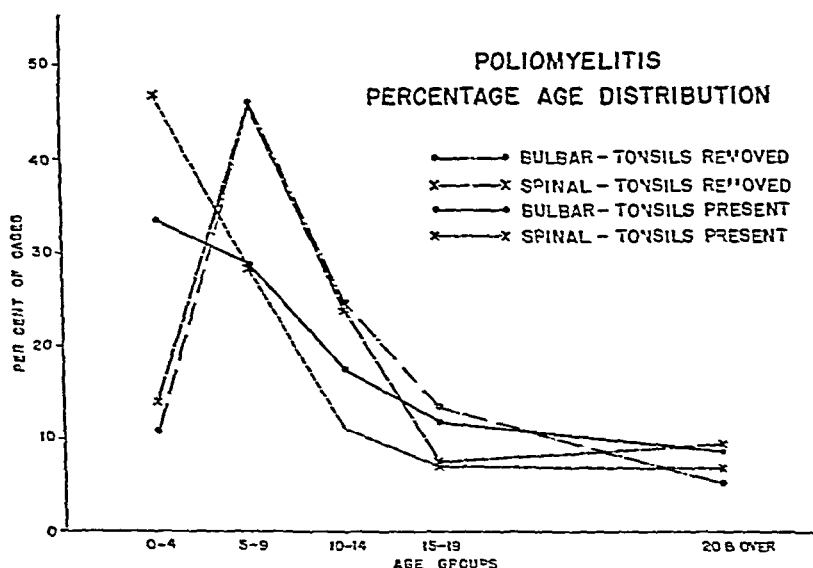


CHART 7 PERCENTAGE AGE DISTRIBUTION OF POLIOMYELITIS ACCORDING TO CLINICAL TYPE AND PRESENCE OR ABSENCE OF TONSILS

TABLE 9

Poliomyelitis according to age, tonsil status and clinical type

AGE	TOTAL CASES	SPINAL			BULBAR AND BULBOSPINAL		
		Total	Recent* tonsillectomy	Previous* tonsillectomy	Total	Recent* tonsillectomy	Previous* tonsillectomy
0-4	599	519	3	31	80	10	14
5-9	555	405	5	106	150	27	75
10-14	256	172	1	57	84	2	53
15-19	141	91	0	18	50	2	28
20 and over	121	94	1	22	27	1	11
Total	1 672	1 281	10	234	391	42	181

* Recent tonsillectomy—within 30 days of onset of disease. Previous tonsillectomy—more than 30 days before onset.

sets shows that as would be expected, both forms of poliomyelitis occur on the average at later ages in tonsillectomized individuals, but it will also be seen that the bulbar type occurs at somewhat later ages in both tonsillectomized and non-tonsillectomized individuals.

TABLE 7

Polomyelitis Multiple cases in families according to tonsil status and clinical type

NUMBER OF FAMILIES	NUMBER AND TYPE OF CASES		BULBAR			SPINAL			REMARKS
	B	S	Recent* tonsillectomy	Previous* tonsillectomy	Tonsils present	Recent* tonsillectomy	Previous* tonsillectomy	Tonsils present	
1	5	0	5†	0	0	0	0	0	†6th child no operation, did not have polomyelitis †2 brothers and 1 stepsister †Same family, †same family
1	3	0	3†	0	0	0	0	0	
2	2	0	2†	0	2†	0	0	0	
1	2	2	0	2	0	0	1	1	
9	1	1	0	4	5	0	1	8	
1	1	2	0	0	1	0	1	1	
1	1	3	0	1	0	0	0	3	†Not same family
30	0	2†	0	0	0	2†	5	55	
46			10	7	8	2	8	68	

B = Bulbar S = Spinal

* Recent tonsillectomy = within 30 days of onset of disease, previous tonsillectomy, more than 30 days before onset

TABLE 8

Polomyelitis Multiple cases in families according to age, tonsil status and clinical type

AGE	BULBAR			SPINAL		
	Recent* tonsillectomy	Previous* tonsillectomy	Tonsils present	Recent* tonsillectomy	Previous* tonsillectomy	Tonsils present
Under 1			1			1
1						7
2						5
3				2		8
4	1		4		1	2
5			1			8
6	3				2	9
7	2	4	1		1	5
8	2	1			1	3
9	1	1				4
10						1
11	1				1	2
12		1			1	2
13						1
14					1	
15						2
16						2
17						1
18						1
19						
20+			1			4
Total	10	7	8	2	8	68

* Recent tonsillectomy = within 30 days of onset of disease, previous tonsillectomy, more than 30 days before onset

non-tonsillectomized individuals Only one report is available which has a bearing on this question. Top and Vaughan (40), in the Detroit epidemic of 1939 studied various factors with relation to tonsillectomy, namely, the clinical type of poliomyelitis, age, sex, the period of time tonsillectomy was performed prior to the onset of poliomyelitis, and tonsillectomy histories of groups of control individuals Their figures indicate that for all forms of poliomyelitis, the percentage of individuals giving a history of tonsillectomy at some previous time is considerably higher among the poliomyelitis cases than among the controls in the same areas

The four groups of controls were made up of individuals in different parts of the epidemic areas, as follows "Case controls" were children known to have been in contact with cases; "special district controls," children from the northern portion of the epidemic area, where the first cases occurred and the attack rate was highest and the economic status low, "west side controls" an area where but

TABLE 10

Poliomyelitis in Detroit, 1951—Cases, deaths and controls by tonsillectomy status*

	TOTAL	NO TONSILLECTOMY		TONSILLECTOMY	
		Number	Per cent	Number	Per cent
All cases	521	306	58.7	215	41.3
Deaths	23	3	(13.0)	20	87.0
Case Controls	497	364	73.2	133	26.7
Special District Controls	129	113	87.6	16	12.5
West Side Controls	167	138	82.6	29	17.4
Children's Inst. Controls	141	89	63.1	52	36.9

* From Top, F. H., and Vaughan, H. F. *Epidemiology of Poliomyelitis in Detroit in 1939*. Am J Pub Health, 31: 777, 1941

few cases were reported and the economic status was low "children's institution controls," children found in homes in the immediate vicinity of a children's institution where a small outbreak occurred, and where the economic status was good

In Table 10 the tonsillectomy status of all cases, fatal cases and controls is given.

Among the 23 deaths, 20 or 87 per cent had had a tonsillectomy at some time or other Among the 521 cases (including deaths) tonsillectomy had been performed in 41.3 per cent The authors do not specify whether the fatal cases were the spinal or bulbar type of the disease Other data presented in this paper indicate a greater frequency of the more fatal bulbar form of the disease in tonsillectomized individuals, and it can be inferred that the Detroit deaths probably include a high proportion of bulbar cases

SUMMARY AND DISCUSSION

In the data given by Top and Vaughan, a history of tonsillectomy is more frequent in all cases of poliomyelitis than in the several sets of controls in the

That the increased incidence of bulbar poliomyelitis in tonsillectomized individuals is not a function of age alone is shown in Tables 8 and 9 and Chart 8. While there is an increase in bulbar poliomyelitis from the younger ages to the age group 15 to 19 (it is not clear whether the decrease in the frequency of bulbar poliomyelitis in adults may not be due to the paucity of the figures), in all age groups the percentage of cases which are bulbar is significantly higher in tonsillectomized than in non-tonsillectomized individuals.

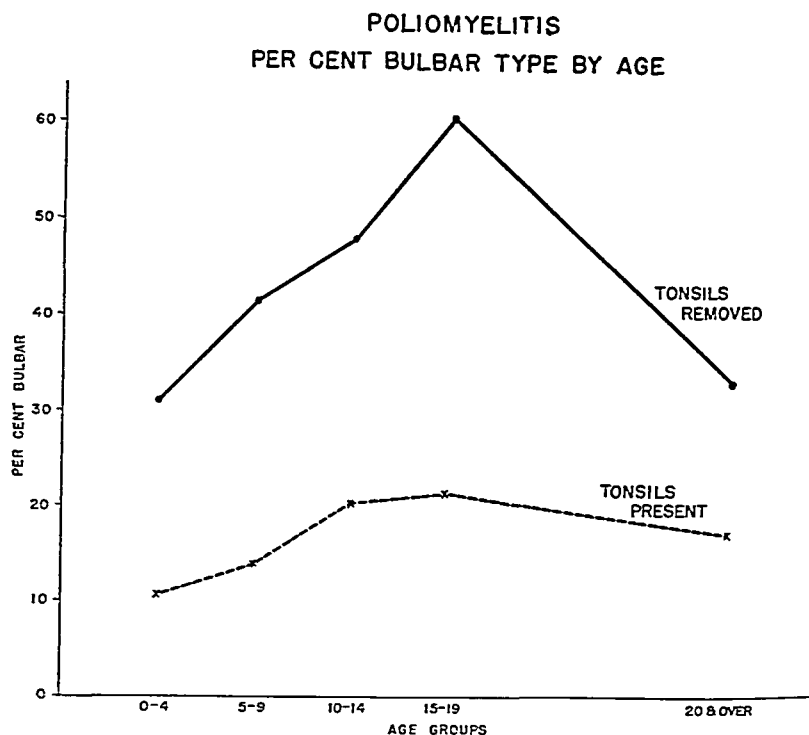


CHART 8 PERCENTAGE OF POLIOMYELITIS CASES IN EACH AGE GROUP WHICH WERE BULBAR IN TYPE ACCORDING TO PRESENCE OR ABSENCE OF TONSILS

VI THE ABSENCE OF TONSILS AS A PREDISPOSANT TO CLINICAL POLIOMYELITIS

Aside from cases of bulbar poliomyelitis following tonsillectomy by a specific interval, none of the data tabulated so far in this paper afford an indication as to whether the absence of tonsils predisposes to paralytic poliomyelitis—bulbar or spinal—upon exposure to the virus. It would appear, in view of the fact that the frequency of the absence of tonsils in non-paralytic poliomyelitis almost exactly equals that for the spinal and bulbar forms combined (Table 6), that the absence of tonsils does not predispose to paralysis in poliomyelitis, but rather is a determinant as between the spinal and bulbar types of the disease in paralytic poliomyelitis.

None of the data presented here permit any expression of the frequency of the occurrence of paralytic poliomyelitis in tonsillectomized, as compared with

The coincidence of the season of prevalence of poliomyelitis with the time of year during which larger numbers of elective operations are done would appear to account for the more precipitous seasonal occurrence of bulbar poliomyelitis following recent tonsillectomy than is seen in poliomyelitis in general.

The data included in this paper, comprising reports of the occurrence of bulbar poliomyelitis following recent tonsillectomy from the literature from case records in Massachusetts and Vermont and from personal communications, show that this form of the disease predominates over spinal poliomyelitis in the group of cases occurring within 30 days after tonsillectomy by about 5 to 1. Furthermore the bulbar cases are concentrated within a specific interval of 7 to 21 days after the operation as compared with the random distribution of bulbar cases occurring in the 30-60 day period and of spinal cases throughout the whole 60-day period. Thus bulbar cases following recent removal of tonsils to a large extent occur after an interval corresponding to the incubation period of the disease.

Epidemiologic investigations gave evidence of widespread infection but limited disease. The distribution of the paralytic disease affords indications that the occurrence of the frank disease in the few of the many exposed to the virus is not only greatly limited but exhibits selectivities which indicate that some added circumstance enters into the determination of the result of exposure to the virus. Certain of these selectivities such as familial occurrence, seasonal and climatic variations in frequency, the association of the paralytic disease with persons of a certain constitutional type, its occurrence during pregnancy, and finally the relationship to tonsillectomy indicate that the added circumstance which determines the result of exposure to the virus resides not so much in parasitic factors or in environmental conditions affecting exposure but in factors of autarcesis in the host.

CONCLUSIONS

The results of the present study are in keeping with other epidemiologic indications that some added circumstance determines the form of the disease which develops upon exposure to the virus of poliomyelitis and that this circumstance resides not so much in parasitic factors or in environmental conditions affecting exposure but in factors of autarcesis in the host.

It is clear from our tabulations that there is a causal relationship between the removal of tonsils and the onset of bulbar poliomyelitis within the time interval corresponding to the incubation period of the disease.

The figures collected do not lend themselves to analysis as to whether or not the absence of tonsils predisposes to clinical poliomyelitis with one exception. In this instance cases of poliomyelitis gave a history of removal of tonsils with greater frequency than controls in the same area. Our tabulations do show, however, that the relative frequency of the occurrence of the bulbar as compared with the spinal form of poliomyelitis is greater at all ages in persons giving a history of previous tonsillectomy.

Because of the numerical considerations, the hazard of bulbar rather than spinal poliomyelitis in tonsillectomized individuals hardly constitutes in itself

same area. These figures, barring any unseen selection—for example, in making up the control groups—would indicate that the absence of tonsils predisposes to poliomyelitis. None of the other records presented in this paper lend themselves to analysis in this respect.

Data concerning the comparative frequency of the bulbar and spinal forms of poliomyelitis in tonsillectomized and non-tonsillectomized individuals (excluding cases occurring within 30 days after the operation) have been collected from articles in the literature, from personal communications concerning the disease in 1941 over a wide range of territory in the United States and Canada, and from case records in Massachusetts 1927–1931 and Vermont 1912–1931. These data all show a higher percentage of the bulbar form of the disease in individuals with a history of tonsillectomy than in those with tonsils present. Non-paralytic poliomyelitis occurs in both groups of individuals with the same frequency as the bulbar and spinal forms combined. These data, therefore, suggest that removal of tonsils is not a determinant between non-paralytic and paralytic poliomyelitis, but rather between the bulbar and spinal forms of the paralytic disease.

That the relatively greater frequency of bulbar poliomyelitis in tonsillectomized individuals is not a function of age alone is indicated by the fact that in all age groups the percentage of cases which are bulbar is significantly higher in tonsillectomized than in non-tonsillectomized individuals.

Because of numerical considerations—roughly 30 per cent of the population have a tonsillectomy at some time and poliomyelitis occurs in only a fraction of 1 per cent—it would be difficult to say to what extent this common operation should be avoided because of the numerically small hazard in respect to bulbar poliomyelitis.

Data from a number of sources, over a period of years, indicate a causal relationship between operative procedures on the nasopharyngeal mucosa and the occurrence of bulbar poliomyelitis following a specific interval. Experiments on the monkey, in which the disease was produced by injecting the virus into the tonsillar region, indicated to one observer that it would be expected that in the human being bulbar poliomyelitis following removal of tonsils would occur when the virus was already present at the time of the operation, which is in accord with the observed occurrence of the disease following the operation at a specific interval.

Operative procedures, such as tooth extractions, have been noted by a number of observers to precede shortly the onset of poliomyelitis. However, since but few cases follow this common procedure, since a specific interval is not present, and since no particular form of the disease is indicated, it would appear that this circumstance belongs to the category of miscellaneous precedent events which have no etiologic significance.

Our series includes a small number of cases of bulbar poliomyelitis following adenoidectomy alone after the specific interval observed in the majority of bulbar cases following tonsillectomy. From the data available, it is not entirely clear whether the tonsillectomy or the adenoidectomy is the associated factor.

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a contraindication to the operation. Although the risk should be recognized, the decision for the operation should rather be based upon the indications in the individual case.

The selectivity seen in the occurrence of bulbar poliomyelitis following tonsillectomy and its relatively more frequent occurrence in tonsillectomized individuals comprise a demonstration that the nasopharyngeal mucosa may be the locus of at least one added circumstance which determines the outcome of exposure to the virus, and is important not only as indicative of the *modus operandi* of autarcesis, but as providing a means of prevention. Since this operation is practically always elective as to time, changing the season when it is done, so as not to coincide with the season of poliomyelitis prevalence, would eliminate numbers of cases of the distressing and highly fatal bulbar form of the disease.

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ON THE PATHOGENESIS OF PARALYSIS AGITANS (PARKINSON'S DISEASE)

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HISTORICAL AND CLINICAL

One hundred and twenty-five years have elapsed since James Parkinson published his immortal essay on the shaking palsy in 1817 (1). So perfect was the picture which Parkinson drew that little has been added to the clinical description but this is not true in regard to the pathology. Parkinson himself unaided by previous inquiries immediately directed to this disease and not having had the advantage in a single case, of that light which anatomical examination yields, was compelled to offer opinions and not facts and one of the main objects of publishing his study was that friends to humanity and medical science might be excited to extend their research to this malady.

The syndrome was characterized in his opinion by 'involuntary tremulous motion with lessened muscular power in parts not in action and even when supported with a propensity to bend the trunk forwards and to pass from a walking to a running pace the senses and intellects being uninjured'. The beginning of the disease is slight and nearly imperceptible and so extremely slow is its progress that it rarely happens that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are a slight sense of weakness with a proneness to trembling in some particular part sometimes in the head but most commonly in one of the hands and arms. These symptoms gradually increase in the part first affected and at an uncertain period but seldom in less than twelve months or more the morbid influence is felt in some other part. As the disease proceeds new inconvenience is experienced. The hand fails to answer with exactness to the dictates of the will. Walking becomes a task which cannot be performed without considerable attention. The legs are not raised to that height or with that promptitude which the will directs so that the utmost care is necessary to prevent frequent falls. Later on the fingers cannot be disposed of in the proposed directions and applied with certainty to any proposed point. Writing can hardly be accomplished and reading from the tremulous motion is accomplished with some difficulty. These symptoms are in the first period temporary, but later the tremulous motion of the limbs rarely ceases and a new symptom involving the posture becomes obvious. The propensity to lean forward becomes invincible and the patient is thereby forced to step on the toes and fore part of the feet whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face. In some cases the patient can no longer exercise himself by walking in his usual manner but is thrown on the toes and forepart of the feet being at the same time irresistibly

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The separation of palpitatio of the limbs (*tremor coactus* of Sylvius de la Boë) from tremor is the more necessary to be insisted on since the distinction may assist in leading to a knowledge of the seat of the disease. In shaking palsy the tremulous motions occur while the affected part is supported or unemployed, and being even checked by the adoption of voluntary motion whilst in the other type of tremor the tremor is induced immediately on bringing the parts into action and ceases when the voluntary exertion for moving stops or the part is supported but returns when the limb is moved. Thus an artist, afflicted with the malady here treated of whilst his hand and arm is palpitating strongly will seize his pencil and the motions will be suspended allowing him to use it for a short period but in tremor if the hand be quite free from the affection should the pen or pencil be taken up the trembling immediately commences.

As a second point of importance Parkinson emphasized the propensity to bend the trunk forward and the tendency to pass from a walking to a running pace. The stiffness of the patient affected with Parkinson's disease is nowadays termed rigidity and well distinguished from "spasticity" occurring in true palsy. *Rigidity* (4) is a state of fairly steady muscular tension involving both flexors and extensors slowing up the voluntary use of the limbs and causing resistance to passive movements it may be as great against flexion as against extension. *Spasticity* is a state of slight or severe sustained contraction in the antigravity groups of muscles causing postural extension in the leg and slight flexion in the arm. When the muscle is passively stretched the spasticity resists to a certain point and then relaxes. If the limb is then left in the new position it holds there like a clasp knife. The deep reflexes are always increased often to the point of sustained clonus. *Cogwheel rigidity* (Negro's (5) sign) is a special type of rigidity on passive motion against muscular tension the muscle feels as if it gave way in a series of steps as if the manipulator were moving a limb attached to a heavy cogwheel. This sign has become one of the most important symptoms of the extrapyramidal disorders being present in their early stages before many other symptoms have developed.

In regard to another symptom described by Parkinson the disorder of the handwriting there is a variety of phenomena. The commonest is micrographia. The patient starts his writing with normal proportions but the letters become progressively smaller and finally the handwriting fades out in an unintelligible scribble. Eventually writing becomes impossible.

Summarizing one can say that Parkinson created a well defined clinical entity characterized by a slow insidious beginning and progress coarse tremor which is more marked during rest than in motion general rigidity poverty of motions inability to associate movements shifting of the center of gravity with pro and retropulsion salivation seborrhea vasomotor and other autonomic changes.

In the following century the clinicians were especially concerned with the distinction of this disease from multiple sclerosis especially Charcot dealt extensively with the differential diagnosis. Nowadays the difference between paralysis agitans and multiple sclerosis is well established. On the other hand the clear-cut pathological entity of shaking palsy has faded away in recent years.

impelled to take much quicker and shorter steps, and thereby to adopt unwillingly a running pace. In some cases it is found necessary entirely to substitute running for walking. As the disease proceeds towards its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent. The power of conveying food to the mouth is impeded so that he is obliged to consent to be fed by others. The bowels, which had been all along torpid, demand stimulating medicine of very considerable power. The words are now scarcely intelligible. The actions of the muscles of the tongue and pharynx are so much impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated, and then as difficultly swallowed. Now also, from the same cause, another very unpleasant circumstance occurs: the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth."

These quotations, taken from Parkinson's original description, illustrate the keenness of his observation and the incisiveness of his exposition. A few observations have been added in later years. In regard to onset, Mendel (2) called attention to the fact that the extremities which later begin to shake, suffer from rheumatoid pains, these may precede the onset of the tremor for many years. Vasomotor sensations, paresthesias, and trophic changes were also observed as forerunners of the disease. Charles Dana (3), who wrote in 1893 the first American study of paralysis agitans with autopsy observations, emphasized "a class of phenomena which, I think, deserves more attention than it has received is that pertaining to the vasomotor system and the blood. Very soon, often within six months of the inception of the disease, there appears a peculiar flushing of the face which gives the patients, along with the facial rigidity, a most characteristic physiognomy. There is apparently also an increase of vascularity in the skin which causes sensation of heat and fever. Sphygmographic tracings show unusual amplitude of curve with evidence of considerable vascular fullness. I believe these are all the evidences of a pretty general vasomotor paralysis, which affects the skin, muscular systems, spinal cord, and nerves. In a certain proportion of cases of shaking palsy attacks of purpura haemorrhagica occur."

Although Parkinson recognized well the disorder of posture, he did not mention the motionlessness of the face, the mask-like appearance which has become one of the fundamental diagnostic signs. Many recent authors have emphasized the stillness of the patient, especially the lack of motion of the face and eyes, winking becomes a rare occurrence. The patient avoids turning his head and prefers to move his entire body around his axis rather than to move a particular part of his body.

In an analysis of the pathognomonic symptoms, Parkinson placed special emphasis upon the kind of tremor encountered in this disease. It is unfortunate that this analysis was neglected in later years. He adopted the distinction (made by Sylvius de la Boe) between those tremors which are produced by attempts at voluntary motion and those which occur while the body is at rest.

multiple sclerosis are in the brain and not in the spinal cord Oppenheim (10) in 1908 said that little was known about the pathology of this disease in the majority of cases a post mortem examination revealed nothing

The first person to study the whole central nervous system in a case of paralysis agitans was Borgherini (11) A definite advance was brought about by Jellgersma (12) in 1908 who demonstrated a degeneration of the ansa lenticularis in two cases of paralysis agitans In 1912 and 1913 F H Levy (13) studied twenty-five cases and found degeneration of the large nerve cells of the corpus striatum and nucleus basalis and also alterations in the tissue surrounding the third and fourth ventricles Under the influence of Cecile and Oskar Vogt special attention was centered on the striatum O Vogt (14) wrote about paralysis agitans in his well known paper of 1919 In our seven cases of paralysis agitans we have invariably found—among more or less extended pathological processes in other parts of the central nervous system—a serious alteration of the striatum and in a smaller degree of the pallidum He observed atrophy of the ganglion cells and degeneration of the myelinated fibres in the caudate nucleus small lacunae with softening and hemorrhages and perivascular rarefaction He used the terms *état precrible* and *état criblé* for the condition around the capillaries and the term *état lacunaire* for the perivascular degeneration around the larger vessels (Fig 1)

The most particular theory with regard to the degeneration of the nerve cells of the striatum and its relation to clinical symptoms was developed by Ramsey Hunt (15) He related the chorea syndrome to a degeneration of the small cells of the neostriatum The paralysis agitans syndrome is in his opinion related to the large cells of putamen and globus pallidus the tremor type to the large cells of the neostriatum (putamen) the rigid type to the large cells of the pallidum (Fig 2)

A strong impetus to the study of extrapyramidal pathology came from observations on postencephalitic Parkinson's disease After von Economo had called attention to encephalitis lethargica a number of French scholars pointed to the importance of lesions in the substantia nigra Under their influence investigators of all countries confirmed the observation that in postencephalitic Parkinson's disease the destruction of the cells of the substantia nigra plays a main part in the pathological picture Chart I lists the more important publications on this subject

It is obvious that there is much uncertainty with regard to the localization of the main lesions Although the corpus striatum is mostly involved in some way the lesions in this part appear of less importance in comparison with substantia nigra It is noteworthy however that the medulla the central gray matter around the ventricles and aqueduct and the cerebral cortex have been found pathological in almost all cases where a complete examination has been made

Because of these studies new interest was centered upon 'idiopathic' paralysis agitans French authors who never entirely accepted the conception of C and O Vogt about the striatal lesions felt that the localization of paralysis agitans was identical with that of post-encephalitic Parkinson's disease For

and the use of the term "parkinsonism" is rather indiscriminately applied to any condition where tremor and rigidity are encountered. How far the confusion has proceeded may be seen from a paper which A. Bizezicki (6) published in 1928 on "parkinsonismus symptomaticus". In this publication, he described three cases of undoubted multiple sclerosis because the cases showed marked spastic paralysis, akinesia and "slight rigidity". Parkinson himself was well aware of the fact that tremor and other signs similar to those seen in shaking palsy, may occur in the course of other diseases, especially after a sudden paralysis which is associated with diminution of voluntary muscular action and impairment of the sense of feeling. He also warned against confusing paralysis agitans with the tremor of advanced age and all those tremblings which proceeded from paresis of muscles.

One of the objects of this paper is to show that the syndrome described by Parkinson is the result of interference with certain functional units of the central nervous system. Such interference carries a typical picture of symptoms known as *paralysis agitans*. Variations in this picture are frequent and a large group of cases is somewhat loosely grouped under the term "parkinsonism". When the cause of the syndrome is known or strongly suspected, adjectives such as encephalitic, postencephalitic, arteriosclerotic, senile and syphilitic are used to modify the nouns. In this paper we use the terms "Parkinson's disease" (or syndrome) and *paralysis agitans* as synonymous and we look on the addition of "ism" to Parkinson's name as a bit of rather barbarous medical vernacular.

PATHOLOGY

Review of Literature

Parkinson was not able to make a post mortem examination upon any of his patients and only on "conjectures founded on analogy," he concluded that shaking palsy is a diseased state of the medulla spinalis extending, as the disease proceeds, to the medulla oblongata. For almost a century the interest of subsequent investigators was centered on the spinal cord and the medulla. Redlich (7) in 1894, studied carefully a series of autopsies upon patients with *paralysis agitans* and compared them with cases of senility without shaking palsy. He found in the former an endo- and peri-arteritis with continuation of the "inflammatory" process into the surrounding tissue. The perivascular tissue showed enlargement of the perivascular spaces and sclerosis. He felt definitely that the pathology of *paralysis agitans* was different from that of senility. These observations are somewhat supported by a study of Spielmeier (8) on senile diseases of the central nervous system. He found increased abnau of an amoeboid type, and expressed the opinion that the alterations of *paralysis agitans* are different from those seen in other types of senile diseases of the central nervous system.

At a meeting of the Neurological Society of New York, on April 7, 1903, Bernard Sachs (9) objected to the opinion of Charcot whose idea was that the main point of differential diagnosis between multiple sclerosis and *paralysis agitans* is that in *paralysis agitans* the head is not involved whereas the chief findings of

vessels. He described the lesions as of a caractère disséminé et insulaire. Tremakoff (17) who was the first to insist on the importance of the lesions of the substantia nigra felt that the localization of paralysis agitans and postencephalitic Parkinson's disease was identical. In reply to the criticism of L. Hermitte he said that important factors are time, the physiological state of the patient and the condition of other systems especially the pyramidal tract. L'Hermitte and Cornille (18) had seen the alterations of the substantia nigra in paralysis agitans.

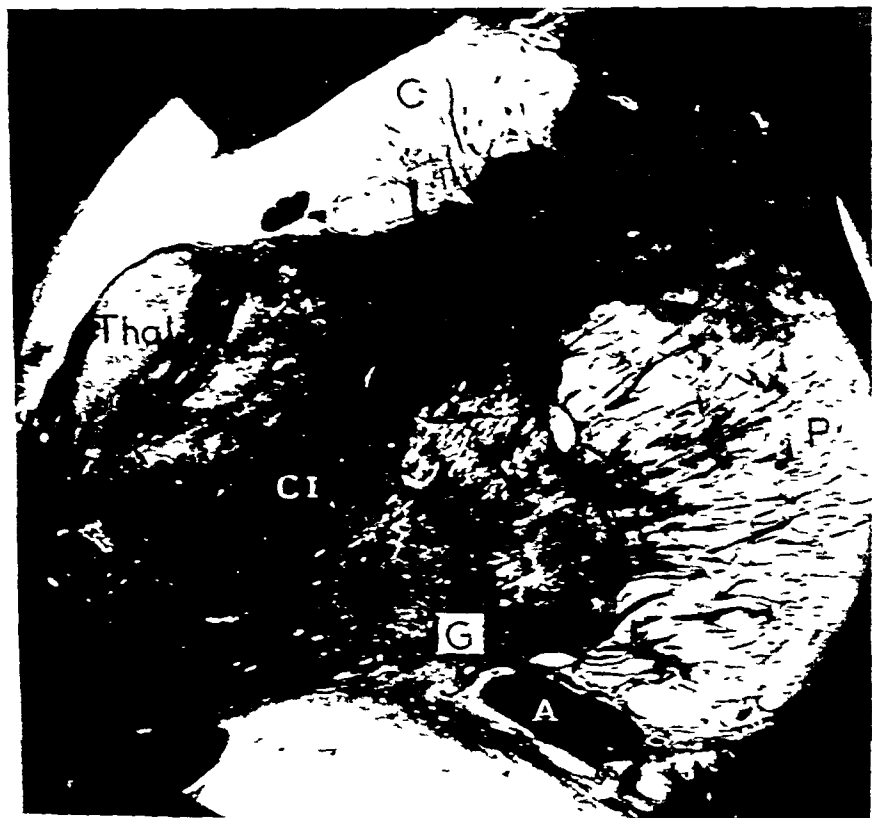


FIG. 2. FOR GENERAL ORIENTATION. FRONTAL SECTION THROUGH BASAL GANGLIA AT LEVEL OF ANTERIOR COMMISSURE.

Picture taken from case 6 (Machinson. For pathology see text).

but they believed them to be non-specific. In a study of seven control cases which did not show the symptoms of paralysis agitans they found similar changes. In paralysis agitans they found lesions in the cortex, in the peduncles, in the pons and especially in the medulla.

A more difficult question which has not yet been settled is whether or not paralysis agitans is frequently due to an unrecognized encephalitis. Signs of an inflammatory process are often present where there is no history of encephalitis. On the other hand, it is the experience of many investigators that after

(16) expressed his belief that the processes were identical and found a constant alteration of the substantia nigra. He found the changes in the lenticular nucleus moderate and not striking and observed moderate calcification of some

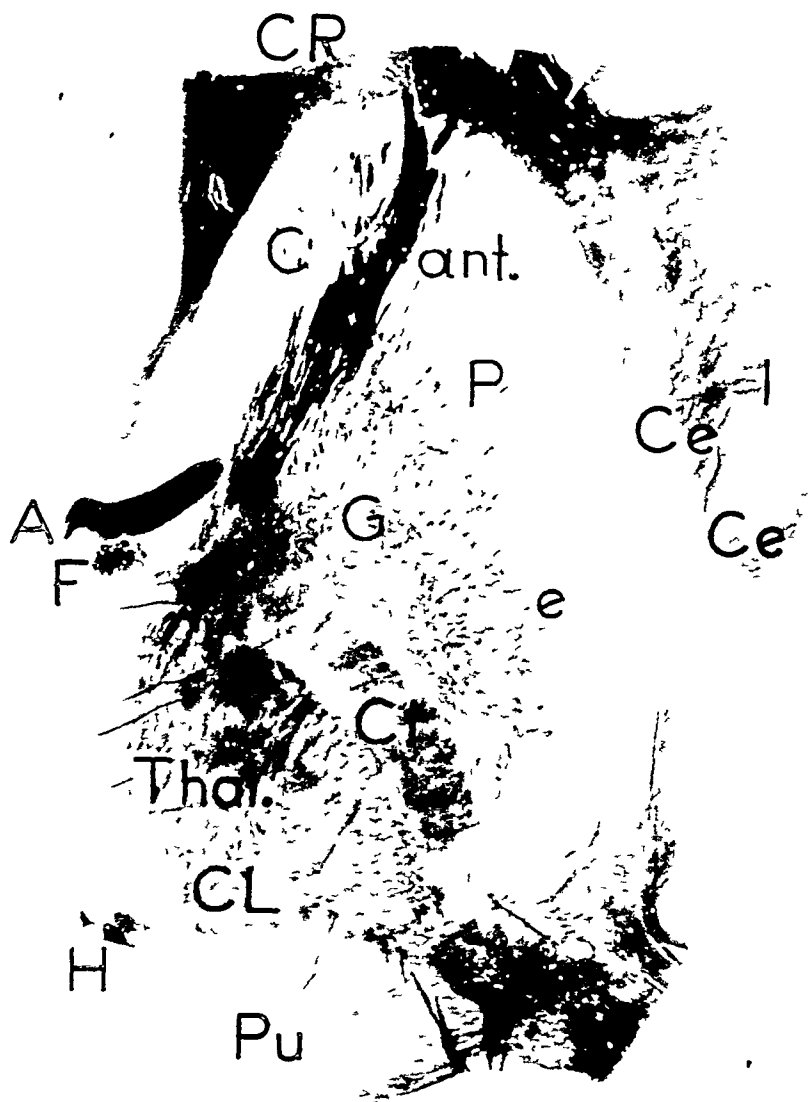


FIG 1 FOR GENERAL ORIENTATION HORIZONTAL SECTION THROUGH BASAL GANGLIA

Picture taken from case 7. Michin preparation. (For pathology see text.) A anterior commissure, C caudate nucleus, P putamen, G globus pallidus, E external medullary lamina, CI capsula interna post limb, F fornix, Pu pulvinar, CL corpus Luysi, H habenular commissure, CR corona radiata, I insula, Cl claustrum and capsula externa, Thal thalamus, ant anterior limb of capsula interna.

tent as the substantia nigra. The globus pallidus seemed to be affected most in the 'idiopathic' cases. The authors expressed the opinion that 'the longer the duration of the disease, the closer does the histologic picture of the cells ap-

CHART 2

Material Publications on the Localization of Parinson's Disease (after 1900)

AUTHOR	PUBLICATION	LOCALIZATION OF LESIONS			SUBSTANTIA NIGRA	OTHER
		Substantia nigra	Pallidum	Putamen		
Brissaud	Rev Neur, 1902	---	-	-	---	-
Yelgersma	Neurol Zbt 1908 925	-	-	-	---	-
Levy, F. H.	Dtsch. Zt. Nervenheilk 1913 50 Berlin-Wien. 1922 Berlin, 1923	-	---	---	---	---
Hunt, R.	Jour Nerv Ment Dis, 1916 11: Brain 1917 49, Am Neur Assn. May 8 10 1916 Arch Neur Psych, Chicago 1933 30, 1932	-	-	---	-	-
Trenschoff	Paris, 1919 Rev Neur, 1920 772	---	-	-	-	-
C & O Vogt	Stauder Heidelberger Akad 1919 J Psychol Neur, 1920 25 Erg H 3	-	---	---	-	-
Lhermitte, et Cornil	Rev Neur 1921 37, 587	---	---	---	-	-
Fox, M.	Rev Neur, 1921 37, 593	---	-	-	-	---
Belchowsky, M.	J Psychol Neur 1922, 27, 233	-	---	---	---	---
Freeman, W.	Am. Ann Clin Med 1925 4, 2	---	-	-	-	-
Hohmann, L. B.	Bull. John Hopk Hosp., 1925 33, 493	---	---	---	---	---
Keschnner M. and Sonne P.	Arch Neurol Psychiatr Chicago, May 1931, 23, 1011	---	---	-	-	-
Heubach	Z-b Neur 1923, 79, 448	-	-	-	-	-
Hassler R.	J Psych Neurol., Leipzig, 1937 43, 287	---	-	-	-	-
Klaus, R.	Arch Psychiatr Nervenheilk 1940, 111, 251	---	-	-	-	-

* Also lenticulars

† Ab atrophic cell degeneration.

‡ But not specific

§ Frontal lobe

proximate that of the idiopathic type. In chronic cases the perivascular infiltration and the abba products in the Virchow-Robin spaces tend to disappear, the cells degenerate and are replaced by proliferative glia, and the myelin sheaths become destroyed, giving rise to état criblé and état marbré. These authors op-

some years the signs of an inflammatory process may cease in encephalitic Parkinson's disease and degenerative changes and scar formation become the main part of the process. In these cases the pathologist cannot prove the in-

CHART 1

Main Publications on the Localization of Postencephalitic Parkinsonism

AUTHOR	PUBLICATION	LOCALIZATION OF LESIONS				
		Sub- stantia nigra	Putamen	Pallidum	Cortex	Diffuse lesions
Tretiakoff, et Bremer	Rev Neur, 1920, 27, 772	+++	-	-	-	-
Lhermitte et Cornu	Rev Neur 1921, 37, 587	+	+	+	+	+
Lhermitte, et Franc- cais	Rev Neur, 1922, 29, 462	++	+	+	+	+
Foix	Rev Neur, 1921, 37, 593	+++	+	+	-	-
Foix, et Nicolesco	Masson et Co Editeurs, Paris 1925	+++	+	+	-	-
Marimiesco	Rev Neur, 1921, 37, 1, 1922, 29, 1012	+	+	+	?	+++
Stern F	Arch Psych Nervenkr, 1921, 161, 43, Berlin, 1922, 2nd Ed, Berlin 1928	*	-	+	++	+++
Goldstein, K	Z ges Neurol Psychiatr, 1922, 76, 627	+++	-	-	-	-
Levy, G	Paris, 1922 (Vigot Freres)	++	+	+	+	++
D'Antony, e Vegni	Il Polichnico 1922, 29 Sez Med, 81, 1923, 30, 195	+++	-	+	-	+
McAlpine, D	Brain, 1923, 46, 255, Brain, 1926, 49, 525	+++	-	-	-	-
McKinlev, C	Arch Neurol Psychiatr Chicago, 1923, 9, 47	+++	-	+	-	+
Luksch, F, und Spatz, H	Münch med Wo, 1923, 1245	+++	-	-	-	+
Hohmann, L B	Bull Johns Hopk Hosp, 1925, 36, 403	+	+	+	+	++
Spatz, H	Ztb Neurol, 1930, 56, 435	+++	-	-	-	-
Keschner, M, and Sloane P	Arch Neurol Psychiatr, Chicago, May 1931, 25, 1011	++	-	+	-	+
Frey, E	Schweiz Arch Neurol Psy- chiatr, 1931, 27, 259-277	++	+	+	+	++
Hassler, R	J Psych Neurol, Leipzig, 1937, 48, 387	+++	-	-	-	-
Klue, R, and Spatz, H	Arch Psychiatr Nervenkr 1940, 111, 251	+++	-	-	-	-

* Not mentioned

flammatory etiology of the condition in spite of the fact that there was a definite history of encephalitis obtained. Keschner and Sloane (19) thoroughly studied seven cases of various types of paralysis agitans and found the substantia nigra involved in six. The locus caeruleus was found involved almost to the same ex-

In 1937 Rolf Hassler (20) published an elaborate paper on the pathology of paralysis agitans and of postencephalitic Parkinson's disease. Hassler concluded that his material confirms the opinion of Tretiakoffi that lesions of the substantia nigra form the underlying pathology of paralysis agitans. He also mentions cellular degeneration in the substantia innominata. The most surprising conclusion of his paper is that the striate body, which the Vogts considered as a main seat of lesions is in his opinion found to be affected in the same way and to the same extent in brains from senile persons who had no motor disorders. Hassler believes that in postencephalitic Parkinson's disease the medial cell groups of the substantia nigra are more affected, in paralysis agitans the lateral cell groups.

When our paper was almost completed, another study on Parkinson's disease appeared from Oskar Vogt's Brain Research Institute, now under the guidance of H. Spatz. In this paper Spatz and Klaue (21) confess their conversion to Tretiakoffi's idea, that the lesions in the substantia nigra are of most importance for paralysis agitans as well as for postencephalitic Parkinson's disease and deny any significance for lesions in the globus pallidus. According to their statement, there are either no lesions or the alterations do not differ from those seen in senile conditions without motor disturbance. The paper confirms the observation, nowadays well established, that lesions in the substantia nigra are invariably found, but the denial of lesions in other sectors indicates that the shifting emphasis is merely a matter of interpretation and is not based on objective observation.

In Chart 2, the main publications on the localization of Parkinson's disease are listed. Brisseau who first mentioned the substantia nigra, found a tuberculoma in the substantia nigra in one of his cases. On the whole the chart is self-explanatory and shows that the observations are more in accord with each other than one could expect from perusal of the literature. The more enthusiastic investigators were prone to emphasize one center while discarding lesions in others, while the more systematic investigators were impressed by the widespread nature of the disease.

NEW CASE REPORTS

Case reports on paralysis agitans are so abundant in the literature that we felt it not necessary to collect as many cases as possible. Eight cases were collected from three large hospitals where the diagnosis was made and these cases will give the opportunity to discuss the problems which are encountered in the pathology of this condition.

The last two cases are included because of the unusual clinical picture but we are aware that a more critical application of the diagnosis of "Parkinsonism or Hemi-Parkinsonism" would question the justification of their presentation.

A brief summary of eight cases¹ is given in Chart 3, and the main problems are stated in the following eight abstracts. Details can be found in the appendix.

¹ We are indebted to Dr. S. B. Wolbach and Dr. T. J. Putnam for the brains of the first three cases, and case four, by courtesy of Dr. Leo Alexander. Case seven and eight through courtesy of Dr. Charles Kubik.

CHART 3

NO	SEX	AGE AT TIME OF DEATH	AGE WHEN PARKINSONISM WAS RECOGNIZED	CHARACTER OF LESIONS	LOCALIZATION
1	M	71	67	Generalized gliosis and degenerative cell changes, some capillary sclerosis and arterial hypertrophy, perivascular necrosis	Substantia nigra, locus caeruleus, pallidum, putamen, subthalamic region, cortex
2	M	61	51	Perivascular round cell infiltration in substantia nigra vessels, venous atony, perivascular enlargement, perivascular necrosis, perivascular gliosis, ependymitis	Substantia nigra, tegmentum of pons, medulla oblongata, locus caeruleus, subthalamic region, pallidum, putamen, cortex
3	M	60	58	Venous atony, arterial hypertrophy, capillary sclerosis, perivascular necrosis, degenerative and gliotic alterations of parenchyma	Substantia nigra, tegmentum of pons, medulla oblongata, locus caeruleus, subthalamic region, pallidum, putamen, cortex
4	F	49	48	Perivascular enlargement, some perivascular round cell infiltration, perivascular necrosis and demyelination, ependymitis, gliosis, patchy parenchyma degeneration	Globus pallidus, putamen, frontal and precentral lobes (substantia nigra not available)
5	M	42	41	Perivascular enlargement, round cell infiltration, ependymitis, varicosity in frontal lobe	Cortex, basal ganglia, substantia nigra, medulla, spinal cord
6	M	18	16	Round cell infiltration, perivascular enlargement, necrosis, patchy parenchyma degeneration, patchy leptomeningitis about frontal lobe with cortical degeneration	Cortex, basal ganglia, substantia nigra, medulla, spinal cord
7	M	63	40*	Vascular atony, status criblé, degenerative changes of parenchyma	Globus pallidus, putamen, subthalamic region, substantia nigra, medulla, spinal cord, cortex
8	M	60	50	Perivascular enlargement, necrosis, status criblé and lacunaire, some round cell infiltration and perivascular gliosis, ependymitis, varicose condition of right temporal lobe	Substantia nigra, globus pallidus, putamen, severe changes in frontal and precentral lobes and temporal cortex

* Probably

posed the view that the neostriatum and pallidum are the predominating sites for the lesions in the "idiopathic parkinsonism" and the substantia nigra in encéphalitic Parkinson's disease

peared again almost free from similar changes. The most outstanding site of the morbid process was found in the right substantia nigra which was reduced one-third in size measuring 10 mm in width while the left measured 15 mm. There was a severe destruction of cells of the lateral and intermediate groups; the process involved also the medial cell groups but to less extent. Changes of importance were found in the globus pallidus where severe demyelination of the fibre bundles especially in the external medullary lamina were disclosed. The lesions were equal on both sides. The putamen and caudate nucleus were essentially negative; the cortex showed patchy atrophy with compensatory fibrosis of the leptomeninges. The vessels were relaxed, the capillaries congested. The perivascular spaces were filled with 'round cells' which were histocytes and not blood elements. The findings revealed severe circulatory deficiency with other changes which are consistent with an inflammatory brain disease but not pathognomonic. The degeneration of the substantia nigra was most marked on the right side and it is of interest to notice that the tremor of the patient was found almost restricted to the opposite side (Fig 3: b and c).

Case 2. This 49 year old woman had shaking palsy of the left leg and foot which developed at an age of about 48 years. Although there was no history of encephalitis the clinicians felt that the picture was that of postencephalitic Parkinsonism. At autopsy the brain showed marked pathology in the globus pallidus on both sides where the fibers were demyelinated and degenerated. Calcification appeared in the form of rings around the vessels of the globus pallidus and calcified particles were found all over the pallidum and to some less extent in the thalamus. The putamen showed pathology of much less degree. The cortex revealed thinning out of the first layer, calcified precipitations in layer five and six in some areas similar to those in the pallidum and patchy degeneration of the nerve cells. The leptomeninges showed irregular fibrotic thickening and the perivascular spaces were filled with blood exudation and abnorm elements. Unfortunately the substantia nigra was not available in this case for microscopic examination. Although the examination did not reveal an active encephalitis the findings were most consistent with post-encephalitic paralysis agitans.

Case 5. In this case a definite history of encephalitis $4\frac{1}{2}$ years before death was given. The patient gradually developed rigidity which interfered with his walking and eating. When he was hospitalized at an age of 42 years a perfect picture of Parkinson's syndrome with rigidity, tremors and movements of trunk and limbs en bloc was present. He showed sympathetic symptoms like ruddy face, marked seborrhea and conspicuous drooling. The autopsy revealed destruction of the substantia nigra, severe destruction of nerve cells in the globus pallidus and putamen and cortical involvement. Most marked were the vascular changes throughout with increased number and size of vessels, great congestion and changes in the vascular walls, hemorrhages in the white matter with iron deposits were numerous, mucin-like deposits and amyloid were found. Of great interest was the development of arteriosclerotic changes in several convolutions of the frontal lobe. This case adds new evidence to the persistence of inflammatory brain changes for several years after encephalitic discharge. The destructions in the substantia nigra in the tissues surrounding the aqueduct and the ventricles in both basal ganglia and in the cortex showed how widespread the involvement of the nervous system was. Of special interest were the vascular changes with the development of a arteriosclerotic condition in the frontal lobes. Similar changes may be seen in cases of paralysis agitans where a definite history of encephalitis is not given (Fig 4: a and b).

Case 6. This patient who died at the age of 15 years went through an obscure disease at an age of seven months when he cried constantly. The end result was a mentally deficient child with over-activity and some behavior problems which are so frequently seen in post-encephalitic conditions of childhood. At the age of 17 he shifted from the restless overactive stage into a typical condition of paralysis agitans with generalized rigidity.

Abstract of Case Reports

Case 1 A former railroad worker, slightly undersized (body length 5 ft 6 ins) developed tremors of hands at an age of 67 years Two years after onset he was first seen on a medical ward At that time he was a poorly nourished man with fixed expression, dry scaly skin, coarse tremors of both hands, slightly more marked on the left side and generalized increased rigidity with cogwheel phenomenon In the course of four years, the tremor increased in intensity and pill-rolling movements were observed The patient died after suprapubic cystotomy, which was performed for his enlarged prostate and difficulties in urination Examination of the brain revealed a rather heavy brain of 1490 grams Microscopic examination showed generalized sclerosis of the brain with increase of all glia types The subependymal glia along the lateral and fourth ventricles was greatly increased The sylvian aqueduct showed a broad layer of marginal glia The nerve cells of the brain showed fatty degeneration all over The substantia nigra cells were still recognizable and not greatly reduced in number but they were degenerated Compared with other nerve cells, the difference in the degree of degeneration was not marked The frontal and pre motor cortex showed macroscopically slight atrophy of the convolutions and microscopically marked sclerosis with atrophy of the nerve cells No senile plaques present In myelin preparations the caudate nucleus, putamen and pallidum showed a darker color than normally Under the microscope the myelinated fibres of the caudatum and putamen showed degeneration but myelin was recognizable on places which are normally without myelin This was especially noticeable near the lateral border and in the rostral part of the putamen (status fibrosus) The perivascular spaces were enlarged and frequently filled with blood exudation and abbaud cells Perivascular necrosis and increase in glia were marked While formation of lacunes was outstanding in the putamen, the pallidum appeared intact The pathological findings indicated a generalized active degenerative process of the brain with marked fatty degeneration of motor cells, increase in glia and a status fibrosus of caudate and putamen The small capillaries were congested, the middle sized vessels relaxed Arteriosclerotic changes negligible

Case 2 This 61 year old patient had a history of at least 10 years of Parkinsonian syndrome affecting both hands and legs He died 10 days after operation for volvulus Autopsy of the brain disclosed the main site of the pathological process in the substantia nigra involving both sides The intermediate cell groups of the substantia compacta were entirely gone, the lateral cell groups destroyed at many levels The medial cell groups were somewhat better preserved although the morbid process was definite and varied at various levels in its degree A second focus of the morbid process was found in both globi pallidi where demyelination of the fibres and destruction of nerve fibres were striking The lateral medullary lamina was degenerated on both sides The striatal fibres in the putamen were demyelinated while the nerve cells were still recognizable although slightly reduced in number The cortex, especially the frontal lobes, showed some areas with a marked reduction of nerve cells and the white core showed bleaching in many sections The leptomeninges revealed patchy fibrotic proliferation The perivascular spaces were enlarged and filled with some abbaud elements There was no evidence of arteriosclerosis The pathological findings indicated a generalized degenerative process with most marked destruction of motor cells in the substantia nigra and degenerative changes of the globus pallidus with no signs of active inflammation (Fig 3d)

Case 3 In this previously healthy and vigorous salesman of 205 lbs a coarse tremor developed at an age of about 59 years The tremor was first restricted to the left hand and showed the characteristics of Parkinsonian tremor During the following years the tremor spread to the left leg The gait became quick, short-stepped and shuffling, his mental reactions became slow and lack of initiative was noticeable Although the post-mortem examination of the body organs revealed generalized arteriosclerosis, the brain vessels ap-

developed was that of generalized rigidity and weakness. The tremor was not an outstanding item in the picture and it is not entirely clear from the history whether the tremors which were observed were of an intentional character or of the "resting" type. Although



FIG. 4

(a) Case 5. Post-encephalitic Parkinsonism. Two adjacent frontal convolutions with vacuolization of white matter. (H and E stain.)

(b) Case 5. Cervical level of spinal cord. Note perivascular round cell infiltration and myelitis. Peripheral demyelination of white matter. (H and E stain.)

tremors, drooling and other symptoms characteristic of this condition. The post mortem examination showed again the wide-spread character of the microscopic lesions with destruction of the substantia nigra, the basal ganglia and severe lesions in the frontal and pre-motor cortex. (Fig 5a, b, c and d)

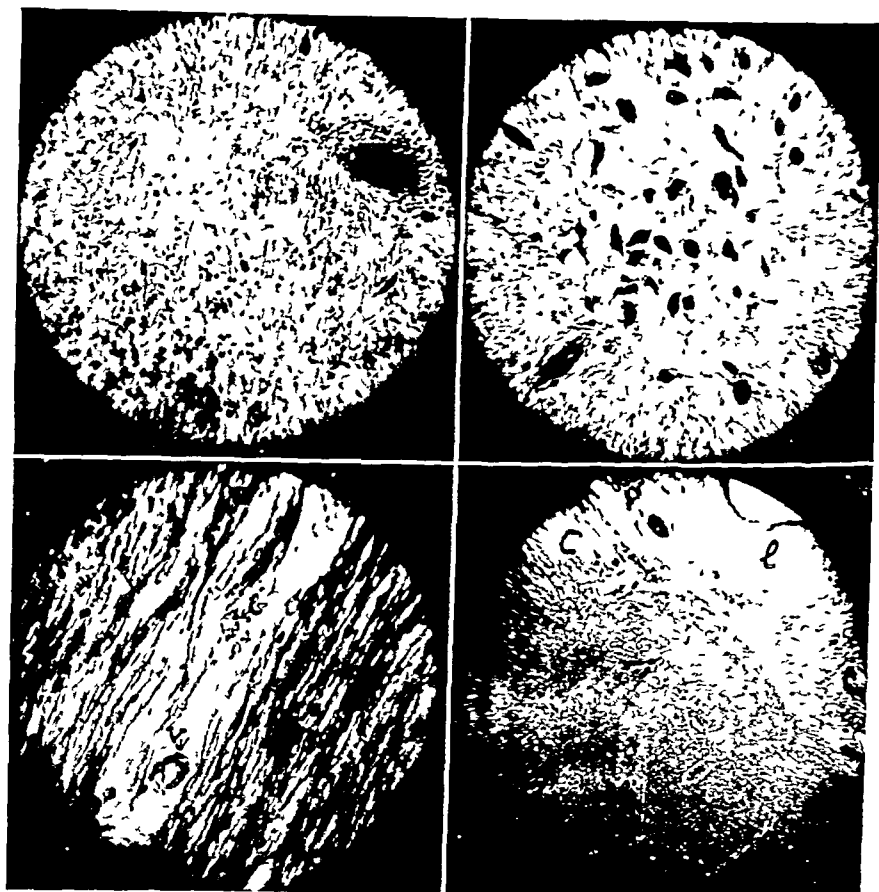


FIG 3

(a) Case 3. Complete destruction of substantia nigra of left side at this level. Note the mesenchymal proliferation around the vessel with slight round cell infiltration and perivascular scarring (H and E stain).

(b) Case 3. Substantia nigra cells of the other side. Some pigmented cells are still present but in a state of dissolution (Nissl stain).

(c) Case 3. Globus pallidus. Note the demyelination with numerous large bulb-like swellings (b) heavy perivascular calcification around small vessels (x) (Weigert myelin stain).

(d) Case 2. Frontal cortex. Note the fibrotic proliferation of leptomeninges (1), atrophy of cortex (c) with ischemic necrosis and cell loss (H and E stain).

Case 7. This patient came under close medical observation at the age of 63 years but the history revealed progressive symptoms since the age of 39. At that time he developed an attack of headache associated with vertigo. Later on he noticed progressive weakness of the legs and loss of strength of the right arm. The neurological picture which eventually

changes of motor cells were obvious all over. The putamen showed a status cribratus with enlargement of the perivascular spaces, hypertrophy of the vascular walls and perivascular necrosis. The pallidum showed marked demyelination. Outstanding was the gliosis around the aqueduct and about the floor of the fourth ventricle. The cortex showed generalized atrophy with widening of the sulci. There were a number of perivascular blood transudations in the basal ganglia and in the mid-brain. This case shows well the difficulties which are encountered in the patient had little medical supervision during life and came rather late under medical care. It is impossible to decide whether or not the whole disease process started with an attack of inflammatory brain disease at the age of 39. The clinical picture which developed later on was more that of general rigidity than that of typical paralysis agitans unless one likes to use the term *paralysis agitans sine agitatione*. The autopsy did not disclose marked arteriosclerosis which could explain the rigidity nor were there definite signs of an inflammatory brain disease. For the diagnosis of "progressive atrophy of the globus pallidus" in the sense of Ramsey Hunt there is little support in view of the widespread lesions in the putamen, substantia nigra, inferior olivary nucleus and cortex. The lesion in the substantia nigra on one side with gliar scar formation and total destruction of nerve cells was suggestive of an old inflammatory disease and it is again noteworthy that the lesion in the substantia nigra was on the left side while the only tremors seen during life were observed in the right limbs of the patient. (Fig. 6a and b.)

Case 8. This patient who died at the age of 60 years had been a backward member of society since childhood. At the age of about 50 he developed attacks of unconsciousness accompanied by convulsions and followed by a period of somnolence. In such an attack he was found stretched out in bed, head and eyes turned to the right, frothing at the mouth, the right leg spasmodically jerking, the left leg and arm stiff. Later in the attack the right arm started to jerk and twitching of the right side of the face was seen. This patient developed a rhythmic tremor of the left arm, hand and head. There was cogwheel rigidity of the left arm. A diagnosis was made of hemi-Parkinsonism and convulsive seizures. The brain showed at autopsy a definite atrophy of the left frontal lobe, in the right temporal lobe a dark area measuring 2 cm. in length and 5 mm. in diameter was found beneath the cortex. The microscopic examination showed wide-spread lesions with patchy degeneration of the substantia nigra more marked on the left than on the right side. In the lentiform nucleus necrosis of the putamen and demyelination of the globus pallidus were marked on both sides. The perivascular necrosis was marked all over the white matter. The pathology in the right temporal lobe turned out to be a venous angioma simplex or cavernoma which showed thrombo-phlebitis. The pathology indicated a severe circulatory deficiency with blood exudation and perivascular proliferation of connective tissue, some "round cell infiltration" and wide-spread degenerative disease of the brain. A difficult question is whether the angioma represented a congenital malformation or occurred as a part of the disease process developing in later life. Some authors are inclined to consider all those angiomas as congenital malformations but observations on angiomas in various organs prove that they may well develop in later life and the senile angioma is a well recognized condition. The difference between a varicose condition and an angioma simplex is impossible to define, the former ends where the latter begins. In our case two facts seem to point to the development in later life. First we saw in case #5 an identical condition in several parts of the cortex as a sequela of an encephalitis and secondly an almost identical enlargement and increase in vascularity, yet of less degree, was observed in many sections of this case. It seems conceivable that the angioma simplex developed from the general stagnation of circulation. On the other hand this patient was somewhat backward from the very beginning which may suggest a congenital malformation. This assumption is supported by the unusual finding of a congenital aneurysm of the aorta and the narrowing of the convolutions of both parietal lobes. It is therefore easily conceivable that there was a small congenital hemangioma in the temporal lobe which was greatly enlarged due to the circulatory deficiency which developed later in life. The pathological findings of the case

"extrapyramidal" disease was obvious, it is not entirely clear whether the picture was that of true paralysis agitans. The pathological findings were also different in several points. Although the substantia nigra showed undoubted signs of unilateral destruction at one level on the left side at many other levels both sides appeared rather well preserved. Fatty

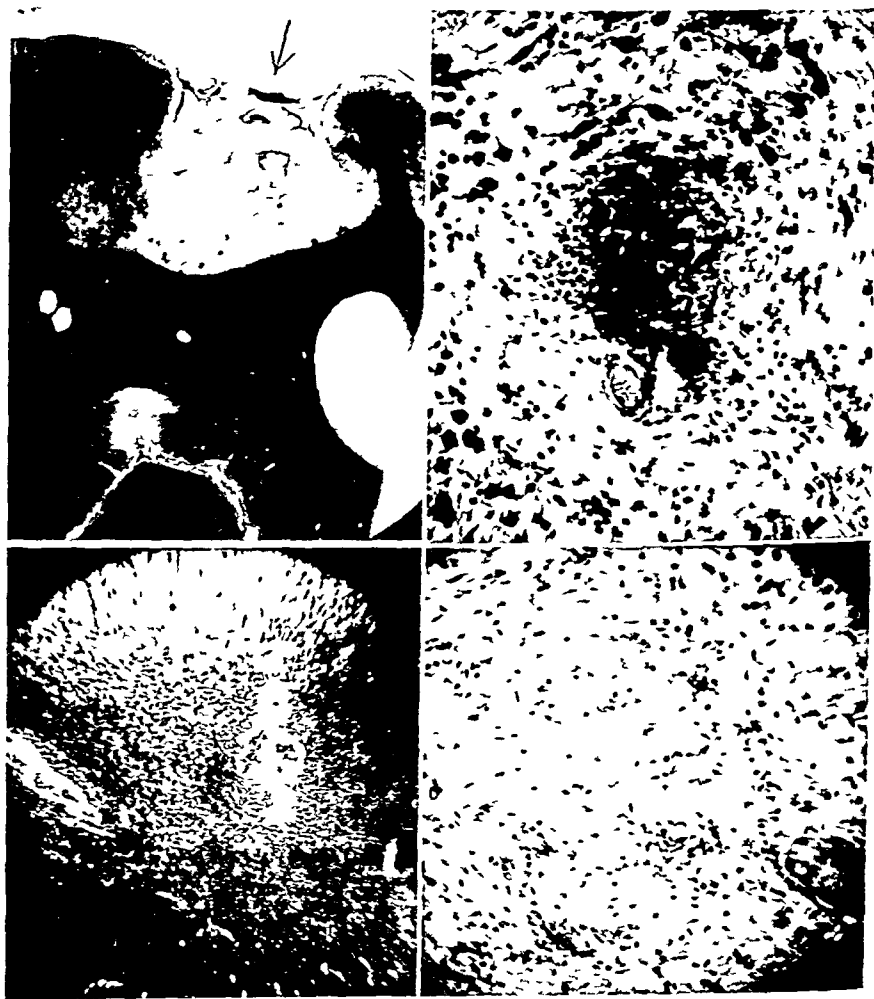


FIG 5

(a) Case 6. Parkinsonism in 18 year old boy. Frontal lobe. Note ulegria (sclerogria) of one convolution with cystic degeneration of cortex and proliferation of leptomeninges (Myeline stain.)

(b) Case 6. White matter of frontal lobe. Note demyelination and perivascular necrosis. Round cell infiltration of perivascular spaces (Myeline stain.)

(c) Case 6. Accumulation of round cells in form of a milium abscess in the neighborhood of a small vessel in the tegmental region of pons. Increased gliosis in surrounding tissue (Nissl stain.)

(d) Case 6. Complete destruction of substantia nigra cells with slight perivascular reaction and general increase of glia (Nissl stain.)



FIG. 7

Case 8. Tuberculous lesion in the cerebellum, showing the typical histology of the disease.

Case 8. Cerebellum, showing the typical histology of the disease. The area shown is a typical example of the disease, showing the characteristic histology of the disease. (Achromic-Kernell stain, x 1000)

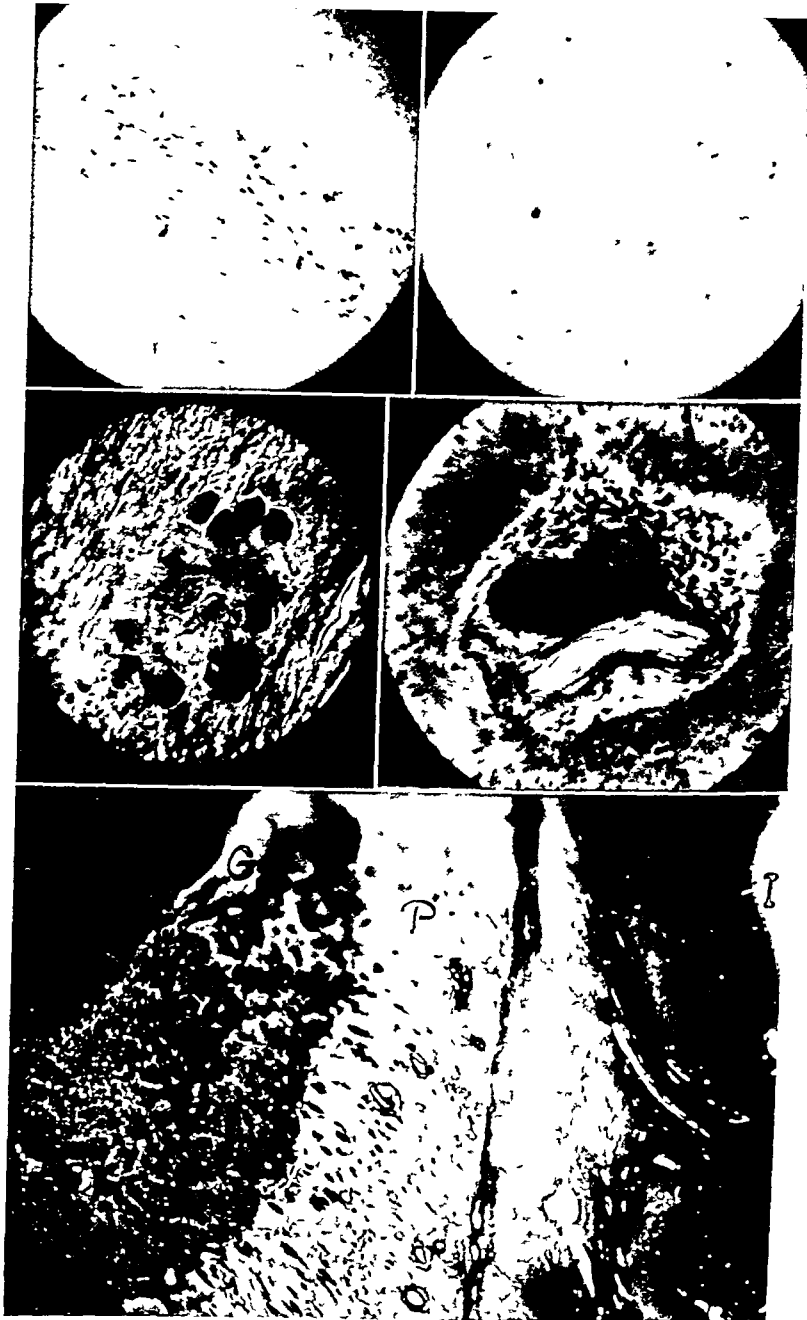


FIG 6

(a) Case 7 At the right hand of observer, the substantia nigra cells (left side of patient) have almost completely disappeared. On the other side the substantia nigra is somewhat better preserved but the cells are small and in a state of dissolution. (Nissl stain.)

(b) Case 7 Glia scars in substantia nigra suggestive of old encephalitic process. (Malloy PHT stain.)

(c) Case 8 Thrombosed vessel in putamen with new canalization and adventitial proliferation. (H and E stain.)

(d) Case 8 Putamen with status disintegrationis. Note the heavy perivascular ring calcification of the small vessels and the status lacunaris in the lateral part of putamen. Perivascular necrosis may be traced deeply into parenchyma. (Mylène stain.) P = putamen, G = globus pallidus, I = insula.

lidum is a separate nucleus ("old striatum") Thus the distinction between caudate and lenticular nuclei is not physiological. Accurately speaking the term "striatum" includes the internal capsule and ansa lenticularis, in fact these are the structures which make the basal ganglionic mass look striated on section. Common usage, however has made the name "neo-striatum" acceptable as meaning the caudate-putamen and "paleo-striatum" the pallidum. The smaller, more caudal nuclei (substantia nigra, reticular formation, subthalamic nucleus

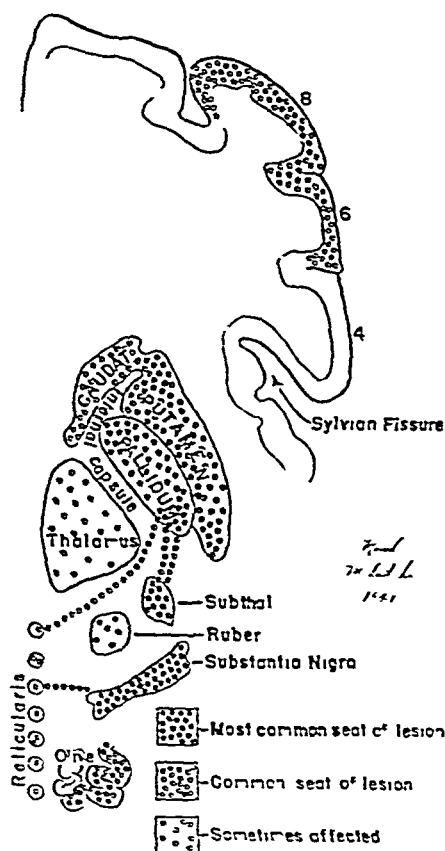


FIG 8. DIAGRAM OF REGIONS OF THE BRAIN WHERE MAIN PATHOLOGY IS TO BE FOUND IN CASES OF PARKINSON'S DISEASE (PARALYSIS AGITANS)

and red nucleus) are basal ganglia closely related to the paleostriatum but they are not in the striatum. The thalamus is largely a sensory organ and the hypothalamus is a way-station for integration of vegetative motor impulses. The extrapyramidal system consists of all the motor nuclei mentioned above plus the "premotor" cerebral cortex (areas 6 and 8) (Fig 9).

There is little doubt that the rather selective involvement of the extrapyramidal system causes the characteristic changes in posture and action seen in

gave ample evidence of involvement of the extra-pyramidal system but the character of the lesion was so confusing that there is no possibility of deciding the etiologic factors which produced the condition (Fig 6c and d and Fig 7a and b)

DISCUSSION

An analysis of the pathogenesis of paralysis agitans should consider (1) the site of the lesions and (2) the character of the pathological process. In the attempt to correlate clinical symptoms with pathology of the brain, one should bear in mind the fundamental conception of Hughlings Jackson (23) that correlation of a symptom with a lesion in the brain does not indicate the localization of function, but does indicate what the remaining parts of the brain are able to perform without that injured region. It is as if one hears the sound of an orchestra change when the violins drop out. The violins alone were not responsible for the former tone color, but their absence allowed the new timbre to appear. The new set-up (Gestalt) not the absent violins is responsible for the new sound. Thus if in the motor concert of the human physiology a tremor appears after a local lesion, the center eliminated by that lesion is definitely *not the source* of the tremor.

In Figure 8 are indicated the main locations of lesions found in our cases of paralysis agitans. One fact is obvious, the lesions do not interfere with the direct transmission of impulses from the motor cortex to the spinal cord. All those pathways which are known as pyramidal tracts are spared. This supports well the clinical observation that pyramidal signs are rare in paralysis agitans and confirms the idea of Parkinson that "the dictates of the will are even in the last stages of the disease conveyed to the muscles." The lesions found in paralysis agitans involve many nuclei of the brain and brain stem, especially those collectively known as the "basal ganglia." Their function can be briefly expressed as the more automatic part of motor activity, that which is nowadays known as "extrapyramidal." Wilson (24) aptly termed it the "old motor system." The nomenclature is so confused that it is important to define how the names are to be used. Although the term is often restricted to the striatum only, we believe that all the diencephalic and mesencephalic nuclei involved in these automatic motor reactions ought to be included under the term "basal ganglia," as follows

Basal Ganglia Nomenclature

Fore-brain	{	Caudate nucleus	{ Putamen }	New striatum	} Striatum	
		Lenticular nucleus				{ Pallidum }
		Thalamus				
		Hypothalamus				
Mid-brain	{	Subthalamic nucleus (body of Luys)				
		Red nucleus				
		Reticular formation (upper part)				
		Substantia nigra				

It is obvious from the overlapping of the two brackets designating "fore-brain" and "mid-brain" that this is really an arbitrary distinction without much significance. It is better to think simply in terms of cord, brain-stem, basal ganglia and cerebral cortex. Reconstructions of the ganglia show that the putamen and caudate are one continuous nuclear mass ("new striatum"). The pal-

reticular substance of the midbrain are injured. Trunk stimulation also affects the position of the head and other lesser reflexes from deep muscles and body surfaces cause the animal to take a posture efficient for arising. Along with this the eyes working on midbrain mechanisms and in coordination with the hindbrain, set up a train of reflex events which brings a prone animal first to look up then to sit up and then to stand in quick and smooth sequence.

The highest level of the 'old motor system' lies in the striatum. Mammals with the cerebral cortex removed and the basal ganglia intact can walk, run and even jump in an effective though automatic way. All they seem to lack is initiative, spontaneity and memory. In other words they have few and rudimentary conditioned reflexes and do not react in the light of past experience. Such an animal is able to go about but has no direction as to where to go except when immediate strong stimuli are applied. A decorticate cat even when the striatum is injured can perform all the locomotor functions so it is the lower basal ganglia rather than the upper that must be concerned with simple locomotion.

In man the situation is even more complex. At present clinical cases alone give a clue as to the function of the human striatum. In other mammals experiments indicate that the function of the striatum is to elaborate motor behavior of even the more highly integrated types and thus make it smooth and effective.

Although the basal ganglia may function well in decorticated mammals normally they are closely connected with the 'extrapyramidal' part of the cerebral cortex. This consists essentially of areas 6 and 8 of Brodman (26) called by Fulton (27) the 'premotor area'. Area 4 is the well known 'motor area' recognized histologically by the presence of the giant pyramidal cells of Betz. The giant cells of area 4 send fibers mostly to the spinal levels of the opposite side ('crossed pyramidal tract'). From the large motor cells in area 6 some fibers may run through the pyramidal tract to the cord but most of them do not go to the cord at all but stop at various levels in the basal ganglia (Fig. 9). Still others arising from cells in area 6 go to area 4. Most of the axons from the great Betz cells of area 4 go directly to spinal levels passing through the pyramid of the medulla. In that sense they are truly 'pyramidal'. A smaller number of fibers largely from the 'strip area' between areas 4 and 6 go to basal ganglia and hence are 'extrapyramidal'. In area 6 the situation is reversed: most of the fibers go to the striatum, red nucleus or substantia nigra. A few go down through the pyramid to the cord.

Stimulation of area 4 causes remarkably local contraction in small muscle groups or even single muscles. In area 6 electrical stimulation results in much more complex, slow, postural movements involving more muscle groups. Lesions in area 4 if small and away from the strip area can cause flaccid paralysis in monkeys; lesions in the pyramid of the medulla may have the same effect. This can be explained by postulating that since no fibers to basal ganglia are cut no postural mechanisms are released to cause exaggeration of postural reflexes (spasticity). When however, area 6 is injured extrapyramidal fibers are interrupted (cortico-striate, cortico-rubral, cortico-nigral, cortico-pontile tracts).

patients afflicted with paralysis agitans. In order to understand the pathophysiology of this region, it is necessary to describe the anatomy and physiology in more detail.

Physiological Anatomy

Neurologists used to describe the motor mechanism as consisting of two levels: the spino-muscular (or "lower motor neuron") and the cortico-spinal (or "upper motor neuron").² This inaccurate simplification has led to much misunderstanding, for such a conception of the thousands of motor neurons divided into "upper" and "lower" is like conceiving of an army organized only with generals and privates. It would be a jerky, incoordinate organization at best. Smooth function is brought into the locomotor mechanism by the system of automatic centers that subserve the functions of arising (righting reflexes), standing, (postural reflexes) and automatic gait. These centers are the colonels, majors, captains and sergeants, overlooked in the dualistic conception. They make up the "old motor system" that sends coordinating messages to the motor cells of the cord and "final common path." These are just as essential to smooth running as the more direct messages from the headquarters of the "new motor system" in the cerebral cortex.

It is obvious that one must arise before he can stand, must stand before he can walk, and must walk before he can go from place to place. Thus the taking and maintenance of postures are fundamentally important motor functions. In the spinal cord there is little postural activity, but the more highly integrated spinal movements do have simple elements of posture held for a short time if the stimulus is maintained. In the hindbrain are important postural mechanisms which cause slow and prolonged muscular responses. Chief among these is the vestibular apparatus. This maintains a steady contraction of the antigravity muscles, and holds man in his standing position by extension of the ankle, extension of the knee, extension and adduction of thigh, extension of spine and head, with moderate flexion of wrist and elbow, adduction of the arms and flexion of jaw. Modifications of this standing position may be brought about by the neck reflexes. These have as their afferent stimuli the proprioceptive impulses from the muscles of the neck innervated by the upper cervical and the spinal accessory nerves. Thus any change in position of the head in relation to the body causes important changes in the posture of the limbs (25). For example, if the head is rotated so that the chin is toward the left shoulder, the left arm and leg extend, and the right flex.

Whereas antigravity reflexes and modifications of them by posture are controlled largely by the hindbrain, true standing and righting reflexes are controlled largely from the midbrain (subthalamic nucleus, substantia nigra, red nucleus and reticular formation). For example there is the reflex which causes an animal (even when blindfolded) to keep its head rotated in space so that the eyes approximate the horizontal. This reflex is lost if the vestibular nuclei or the

² For a more detailed description see COBB, S. *Foundations of Neuropsychiatry*, Chapter III from which this abbreviation is taken.

example, "spasticity," "rigidity," and "flaccidity" are not used to mean the same thing by the different authors. These have been defined above (see page 97).

Another term that continually disturbs scientific exposition because of inaccurate definition is "inhibition." Usually it is taken to mean *suppression* of a

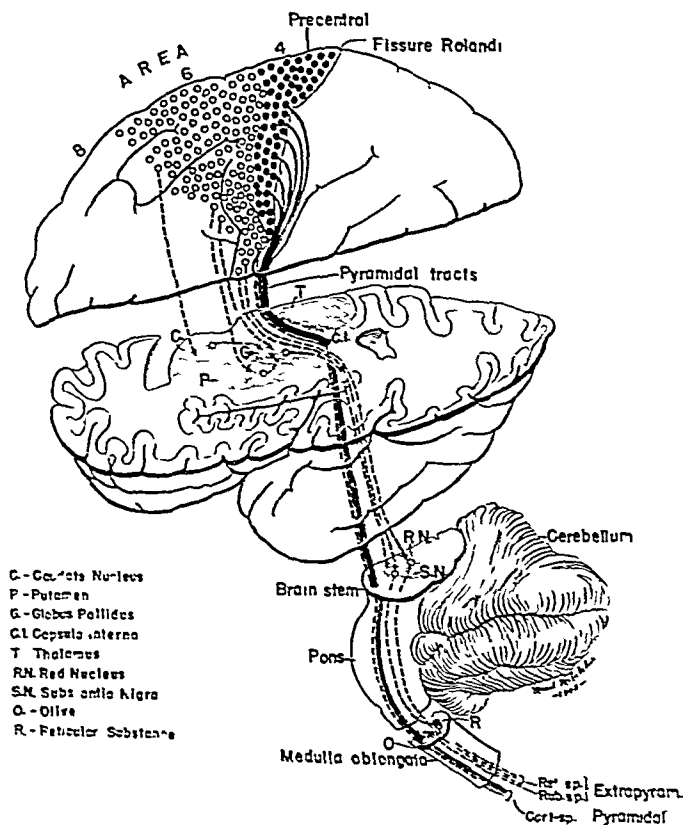


FIG 10 SEMIDIAGRAMMATIC REPRESENTATION OF THE MOTOR SYSTEM IN MAN TO SHOW ANATOMICAL RELATION NOT BROUGHT OUT IN FIGURE 9

There are two main paths for motor impulses from the cortex to end-pool: the "pyramidal" and the "extrapyramidal" systems. The former is a direct, uninterrupted, crossed connection between cortex and spinal motor centers; the latter is a system of short connections between cortex and medulla, an intercalated system of several centers. The reticular formation (cf. fig. 5) is here shown only at one level.

function and, in neurology, suppression by means of nerve impulses impinging on active neurons and decreasing their expression in effector organs (28). The original meaning of the word is "to bridle" or control, as when one is controlling a horse with bit and rein. It does not mean to merely suppress, but also to guide. In this sense it almost exactly expresses the function of cerebral cortical neurons.

releasing postural reflexes with increased muscular rigidity (27). True spasticity occurs when both areas 4 and 6 are injured. The common lesion in man is an extensive one including parts of both areas 4 and 6, so the functional result is a spastic hemiplegia. Thus "pyramidal" meaning "cortico-spinal", and "extra-pyramidal" signifying tracts from the basal ganglia, are terms that are no longer

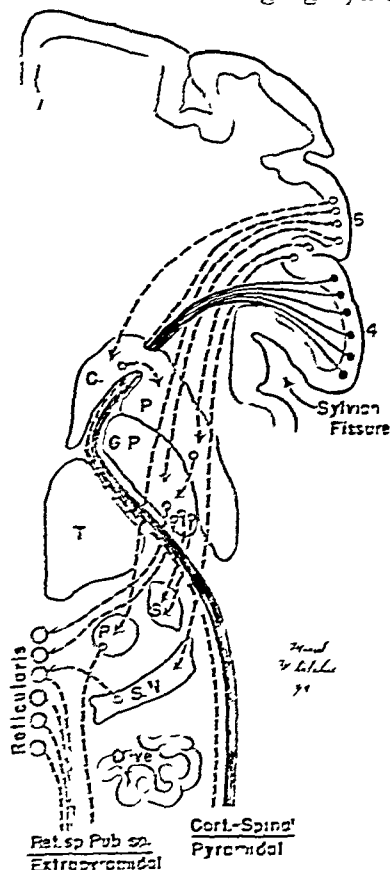


FIG. 9. DIAGRAM OF MAIN CONNECTIONS OF CORTIX AND BASAL GANGLIA

Black lines Pyramidal tracts from cortex to spinal anterior horn cells. *Broken lines* Motor pathways from cortex to spinal cord passing through various centers of the "extrapyramidal" system. 5 Premotor area of cortex. 4 Motor area in cortex. C Caudate nucleus. P Putamen. GP Globus pallidus. T Thalamus. S Subthalamic nucleus. R Nucleus ruber. SN Substantia nigra. Reticularis Column of motor cells in brain stem from mid-brain to upper cord, forming the "substantia reticularis" or "reticular formation".

permissible (27), because the extrapyramidal system is well represented in the cerebral cortex.

The difficulties that arise in the discussion of pyramidal and extrapyramidal paralysis are partly due to the lack of definite usages of words. Not only is there divergence in anatomical nomenclature, but clinical terms are used loosely. For

understood only on the view that they contain elements belonging to the cortical centers ”

With this point of view we agree. New evidence (30) available since Wilson wrote this passage indicates that the function of the striatum is, primarily, to elaborate the simple motor and postural mechanisms of the brain stem into complex automatic motor behavior, and, secondly, to take over highly integrated movements from the cortical motor centers when they have been thoroughly learned (31)

The disorders of the extrapyramidal system which are commonly mentioned in association with paralysis agitans are Huntington's chorea and Wilson's disease. Both diseases have lesions in the caudate nucleus, putamen and globus pallidus and both (like paralysis agitans) have involuntary movements, but the analogy ends here. The common conception that "extrapyramidal" and "striatal" are identical terms is not supported by anatomy and physiology (see page 114). The localization of paralysis agitans as a striatal disease, therefore, is based more on analogy than on definite evidence.

Choreatic movements are jerky, quick, purposeless movements which occur as hyperkinetic phenomena during rest and as interruptions of coordinated motions in action. The patient is unable to maintain a certain attitude for any length of time, his ability to make smooth controlled motions is impaired, the movements appear exaggerated, jerky and impulsive. Relaxation, not rigidity, is the condition of the neuro-muscular system associated with Huntington's chorea as well as with Sydenham's chorea, no changes in posture and no tremor are observed, in short, the clinical picture is quite different from that of paralysis agitans. One would not expect the lesions to have similar localizations. As a matter of fact, Huntington's chorea shows the most marked lesions in the neostriatum. The caudate nucleus and putamen are reduced in size and show cellular atrophy. The lesions are, however, not entirely restricted to this area and involvement of the frontal cortex is invariably found (32, 33). Huntington's chorea occurs in patients who are beyond 20 years of age, mostly between 30 and 40, who have previously acquired normal motor control. The chronic degenerative process gradually deprives the patients of their learned motor control but gives them ample opportunity to develop some compensatory mechanism to partly replace the lost functions.

In Wilson's disease (progressive hepatolenticular degeneration) the patient suffers from increasing rigidity, suppression of normal motility with appearance of involuntary movements and outbursts of laughing. The movements are unsteady and associated with intention-tremor. The face becomes mask-like, the voice inarticulate and mastication is difficult. The onset is much earlier than in Huntington's chorea, mostly in the second decade, but the patients had previously established motor control and appeared normal. The striatum is involved, the lesions consisting of parenchymal degeneration with cavity formation and some glia proliferation. The site of the lesions is especially in the putamen, the pallidum is usually involved and the caudate nucleus is more or less spared. Although Wilson's disease shares with Huntington's chorea the involvement of

on lower centers. This is because the higher³ mechanism adds something new to the functional result, the movement innervated is more skillful, more perfect. In order to do this it must suppress certain parts of the functions of lower centers, but it also elaborates and guides by means of being in closer touch with the associative elaborations of the cortex. Unfortunately, however, the word has come into general use as meaning *suppression*, so we shall give it up when speaking of neural motor mechanisms and substitute the word "control."

Finally we can summarize the function of the extrapyramidal system as follows, Fig. 10. Cortical area 6 is the highest level and controls both the striatum and to some extent cortical cells in area 4. The neostriatum elaborates and smooths out the coarser motor integrations of the paleostriatum. These in turn control the primitive walking reflexes of the subthalamic region (29) which make use of the righting reflexes of the midbrain nuclei and the antigravity reflexes of the hindbrain, largely from the lateral vestibular nucleus of Deiters. The lowest level is, of course, the spinal, where all the extrapyramidal impulses (running down the vestibulospinal, reticulospinal and rubrospinal tracts) reach the "motor pool" about the ventral horn cells and eventually discharge along the final common path. Even this summary is not entirely accurate because a few "extrapyramidal" fibers come from area 6 and, joining those from area 4, travel down through the pyramids of the medulla oblongata and hence are "pyramidal" (See Figs. 9 and 10.)

Clinical Considerations

In comparing the various clinical syndromes related to disease of the basal ganglia, there appear fundamental differences. Kinnier Wilson (24) has repeatedly emphasized three postulates: that histological lesions which are recognized as destructive only explain loss of function, that in the case of multiple lesions, none must be neglected regardless of their seeming unimportance, and that the localization of a symptom is not the same as the localization of a function. He further pointed out that "It is *a priori* highly improbable, and contrary to the dictates of common sense, that motor phenomena so conspicuously diverse and of such varying complexity as myoclonus, tremor, athetosis, chorea, tics, bradykinesia, torsion-spasm, micrographia and palilalia, should one and all be set down to disorder of striatal function. When we remember the histological simplicity and comparative structural homogeneity of the corpus striatum, in contrast with the greater dimensions, much more intricate cyto-architectonic complexity, and far wider connections of the Rolandic motor cortex, the idea of attributing all these disturbances to striatal disease, and of crowding corresponding "centers" into that ganglion, becomes nothing short of ludicrous. Consideration of the intrinsic clinical features of some of the motor disorders put down to striatal dysfunction proves that under no circumstances can they be conceived of as resulting from defect or destruction of identical or similar mechanisms, for while some are physiologically of a high order, others are of a low. Some can be

³ "Higher" meaning more complex and more cephalad in the hierarchy of motor reflex levels.

to 7 per second. The substantia nigra can be ruled out as a source of tremor because it is the nucleus most commonly destroyed, the subthalamic and red nuclei can also be ruled out because they are frequently pathological in cases of paralysis agitans.

For a better understanding we may consider some clinical and physiological observations. The typical Parkinsonian tremor ceases in sleep and in complete relaxation and seems to disappear when a volitional motion is exerted. Between rest and action, the normal person exerts innumerable muscular tensions and inconspicuous movements which adapt him to the various postural conditions of his equilibrium and to the various conditions of his surroundings. They are necessary to prepare the proper position for any response in action. Observation of normal people convinces one that a person when awake is never at complete rest and that the condition of consciousness is normally associated with innumerable motor actions. Several clinicians have emphasized the fact that the Parkinsonian patient, except for his tremor, is immobile in an extraordinary way. He avoids moving or changing his position, he is remarkably slow in adapting to any shift in his equilibrium. As restlessness is accumulated the tremor increases, and it becomes more conspicuous before a volitional motion "breaks through." In the moment of action the tremor disappears, but the action itself is abrupt and not properly controlled. Often the motor output is greater than intended.

The tremor is not really a "hyperkinesia" occurring at rest (like choreatic movements), it is the only expression of activity of a patient who otherwise appears motionless and statuesque. The tremor increases the more restless and tense the patient becomes. It is all the motion the patient has until he breaks through with a voluntary movement. The tremor represents a "marking time" that disappears in action. Essentially the patient with paralysis agitans is *hypokinetic*.

Normal contraction in striated muscle is a tetanic phenomenon. Rapid nerve stimuli at 50 to 100 per second reach a muscle fibre and it contracts steadily for a short time according to the laws of summation, all-or-none response and refractory period. Many individual fibres are stimulated at different times, as one relaxes others contract and take up the load. The result is a smooth, sustained contraction of the whole muscle. A large surface electrode will pick up action-potentials from a contracting muscle that have a rate of over 100 small spikes per second often falling into a rhythm of about 50 larger waves per second. It is only under conditions of abnormal innervation that this tetanus is broken down into an interrupted clonic contraction (36).

Insight into the character of the Parkinsonian tremor has recently been given by Hoefler and Putnam (37) who studied action-potentials in the trembling muscles. "The electromyogram of tremor consists of rhythmic bursts of spike potentials with electrically inactive stretches between. Each burst of spikes corresponds to one phase of the tremor movement. The free interval may last twice as long as the burst of spikes. The rate at which the tremor occurs is on the whole surprisingly regular and uniform for a given patient in different muscle

the putamen, the character and evolution of the lesions is entirely different. This may account for the entirely different clinical picture, but there are also differences in localization as well as similarities.

It is obvious that paralysis agitans has several symptoms in common with Wilson's disease. As far as slow motion, mask-like face and rigidity are concerned, the differential diagnosis of juvenile cases of paralysis agitans and Wilson's disease may be difficult. The main point of differentiation is the type of tremor, which is an intention-tremor in Wilson's disease, while the tremor of paralysis agitans is generally referred to as "resting" tremor. The point is indeed well taken by Parkinson, he put much emphasis on the character of the shaking palsy and made this symptom the head-line of the morbid entity. The tremor is not only the most conspicuous symptom but is of such particular character that it is necessary to analyze it in more detail.

Parkinsonian Tremor

Parkinson emphasized the contrast between tremor during volitional motions and the tremor of paralysis agitans which he called "resting tremor," but analysis shows that the term "resting tremor" is not correct. Moreover this conception of "resting tremor" has misled later investigators to consider the tremor as a "hyperkinesis." If tremor were a "hyperkinesis," it would be hard to understand from what source it comes, unless we assume a cortical "irritation." Such a process is entirely improbable in a chronic disorder that goes on for years. If tremor were a release phenomenon of lower centers, we would have to assume that the lower centers in the brain stem have a rhythmic alternating discharge. Formerly neurologists and physiologists have postulated such rhythmical discharge from rhombencephalic centers (34) explaining the slow rhythm as a release of the lowest form of ancestral vertebrate motion, the steady trunk and fin movements of fishes. Recent physiological experiments do not support this supposition, and at best it was a speculation. If we ascribe tremor to rhythmic discharges of mechanisms of the basal ganglia, these discharges must become pathological either by stimulation (direct irritation), by release of motor intact mechanisms or by disorganization with a new configuration that results in tremor. The irritation theory can be ruled out on the same grounds as irritation of the cortex, i.e., chronicity. If tremor is due to a release of certain basal ganglia by lesions at a higher level, there would have to be certain nuclei that were always found intact and free from lesion in cases of tremor. It is obvious that a tremor lasting for years cannot come from some motor nucleus that is knocked out by a lesion. No nucleus in the basal ganglia is always free from pathological change in cases with rhythmic tremor.

In accepting the release theory one would consider the four nuclei at the lower level as a reasonable source of tremor—substantia nigra, red nucleus, subthalamic nucleus and nuclei of the reticular formation. The latter are largely rhombencephalic and have many functions, so reticular nuclei cannot be ruled out as a possible source of tremor, but much electrographic work has been done on this region (35) and no rhythms have appeared at the Parkinsonian rate of 5

Location of the Lesions

Pathological examination reveals severe lesions in the substantia nigra and wide-spread damage to all those centers which we have defined as composing the system of basal ganglia. Our pathological material also indicates that no case of paralysis agitans is without involvement of the cerebral cortex, especially the frontal areas and area 6. This fact is well recognized for the cases of post-encephalitic paralysis agitans, our own investigation and several other publications (see Chart 2, page 103) indicate that the same is true for Parkinson's disease. The profound patchy demyelination of the frontal lobes, the status lacunaris seen in the white matter, the patchy degeneration of nerve cells, the atrophy of convolutions and the fibrotic thickening of the leptomeninges in many cases overshadow the lesions seen in the basal ganglia. Certainly one is not justified in putting great significance on one group of lesions and disregarding those found in other locations. It is such unfair emphasis that upholds the theory that the basal ganglia produce tremor and that the whole picture of extrapyramidal dyskinesia is due to a lesion in this region alone.

As we previously emphasized it is important to consider the parts which remain normal and are therefore able to maintain functional activity. Microscopic examination of the brain confirms our theory of the integrity of the motor cortex with its Betz cells. This explains why paralysis agitans rarely occurs in the common senile degenerations in which the cortex is most heavily involved, because in paralysis agitans the motor cortex ought to be fairly well preserved. In Parkinson's disease, arteriosclerotic alterations of the cortex are almost absent, a fact which attracted our special attention and is also mentioned by Spatz (21). It seems probable that the tremor of paralysis agitans can only occur when the motor cortex is largely intact. According to our analysis, the tremor of paralysis agitans is due to a condition in which the lesions are neither so widespread as in some senile diseases nor restricted to any single center like putamen, pallidum or substantia nigra. If we are right in considering hypersynchronization of motor nerve-impulses as the physiological explanation of the tremor, then the anatomical explanation would seem to be as follows. Area 4 and the pyramidal tract must be functioning well, area 6 and the basal ganglia must be partially destroyed but not wholly. In other words cutting out some of the extrapyramidal control is necessary for the genesis of the tremor, cutting out a large part of it suddenly (Klemme's operation 39) stops the tremor temporarily, cutting out most of the control by sectioning the ansa (Myer's operation 40) seems to stop the tremor permanently in certain cases. It is probable that certain of the basal ganglia are more important than others in this connection but the data are as yet insufficient to justify specific localization.

In summarizing the problem of localization one can point out that paralysis agitans is an extrapyramidal disorder involving the large group of centers and fibre connections which subserve the numerous automatisms essential to normal motor performance, they integrate skilled motor acts and locomotion and stabilize posture. Because of the extent and the state of high differentiation of the extrapyramidal system, there are even more variations in symptomatology amongst

groups and at different times, months apart " The average rate in this long series of cases was 5.5 per second with a range roughly from 4 to 8 per second

If the action potentials of voluntary movements of Parkinsonian patients are studied, they reveal essentially the same pattern "Instead of a continuous sequence of tall spikes the action potentials are grouped in bursts at a rate of about 6 a second, while smaller potentials apparently keep up the continuity of innervation between them In some cases the continuous sequence is abolished and replaced by discrete bursts of spike potentials separated by stretches of electrical inactivity " The studies of Hoefer and Putnam also showed that voluntary innervation produces electrical activity in antagonist muscles This secondary activity may become almost as strong as the primary activity accompanying the active effort in the protagonists

Most important of all is the synchronization of nerve impulses which occurs in paralysis agitans Hoefer (38) points out that if one has normal muscular reaction and smooth movement, the impulses are out of phase Three electrodes registering in one muscle will show non-synchronizing impulses, but the muscle as a whole has smooth contraction because there is a smooth alternation of units In paralysis agitans this alternating action is abolished and electrodes in different points of the muscle register electric activity at exactly the same time, abnormal synchronization of motor impulses has taken place

In their discussion Hoefer and Putnam expressed the belief that "the tremor impulses are conducted along pyramidal tracts " We would prefer to say that the impulses which cause tremor are conveyed through the pyramidal tracts The impulses are not abnormal, their timing is at fault This observation offers a key for a final understanding

Our explanation can be expressed as follows In the Parkinsonian tremor those cortical impulses which are conveyed through the pyramidal tracts reach the "end-pool" while the discharges conveyed through the extra-pyramidal pathways (which distribute the phasic innervation and guarantee smoothness of action) are out of order The tremor is due to the fact that transmission of the motor nerve-impulses is reduced and simplified to the primitive pattern of synchronized innervation, alternating in antagonistic groups of muscles This results in to-and-fro motion while the multidimensional stabilization in space is lacking Thus Parkinsonian tremor is due to a diffuse disorganization of the extra-pyramidal motor mechanism causing a new configuration of motor paths with a primitive type of function The long cortico-spinal fibres are largely intact, the internuncial paths between cortex and spinal cord are damaged The cortex is partly deprived of its striatal connections, which play an important part in distributing motor activity, and spinal centers are partly deprived of their connections with their higher regulatory centers

To corroborate this theory of the pathophysiology of Parkinsonian tremor, one would expect to find at autopsy (1) a relatively well preserved motor cortex, (2) well preserved motor centers in the spinal cord, and (3) lesions in the extra-pyramidal system We will see that our pathological study is well in line with this theory

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the extrapyramidal disorders than among pyramidal disturbances. In regarding such a complex clinical picture as paralysis agitans, one should expect from the very beginning that numerous systems would be involved. Our pathologic studies and survey of the literature offer ample evidence that this assumption is true. In all the cases of paralysis agitans we have seen lesions are distributed as shown in Fig. 8 but mentioning also the locus caeruleus, the tegmental region, the dorsal vagus centre, and parts of the temporal cortex. The combinations vary, but there is not a single well studied case in the literature where one lesion alone could explain all or even most of the disorder. Whenever an author gives such overemphasis to one center, there is evidence that he tried to force the facts into a scheme by neglecting others which did not fit into his prejudiced conception. Recent papers have confirmed the observation that the substantia nigra is not only affected in postencephalitic paralysis agitans but also in Parkinson's disease. Nevertheless those papers do not prove that lesions in other centers are of no significance. The authors do not take into consideration the probability that it is the varying combination of lesions, rather than the defect of a single center, which produces the variation in symptomatology. Moreover some of them do not seem to realize that the syndromes are not the direct product of one lesion injuring a motor nucleus, but arise from the combined attempt of the remaining normal nuclei to approximate a useful motor function.

Nature of the Pathological Process

Most of the pathological studies dealing with paralysis agitans have dwelt almost exclusively on the localization of the lesions, little attention has been centered upon their character. Yet there is evidence that even with identical localization the effect of a lesion may be quite different according to the character of the process and the degree of acuteness or chronicity. Of the eight cases which we have described, only one (case #5) had a definite history of encephalitis. This case is of interest because it demonstrated so well the fact that in chronic encephalitis the vascular lesions may be of most importance while the proper signs of inflammation, although present, may be of minor concern. These vascular lesions consisted of enlargement of the perivascular spaces and perivascular necrosis. In parts of the cortex vascular congestion with stagnation and relaxation of the vessels seems to have led to a varicosis in several convolutions. The varicosis appeared as a most extreme degree of the status lacunaris which was to be found in many sections of the brain.

Although in case 6 there was no history of an encephalitis, the pathological picture indicated an inflammatory brain disease with the same profound effect upon the vascular system and resulting perivascular necrosis. For these two cases, we may, therefore, accept the etiology of an encephalitic process and both cases would go under the heading of postencephalitic paralysis agitans.

It is also known that arteriosclerosis under certain conditions may produce the picture of paralysis agitans. In some instances in the literature (41) the history indicates that the symptoms did not develop before a general arteriosclerosis took place and the course of the disease indicates the dependence on an

arteriosclerotic malnutrition of the brain. How many cases of Parkinson's disease fall into the group is hard to determine. In many cases the onset of the disease seems to have occurred long before arteriosclerotic alterations developed. As early as 1912, F. H. Lewy pointed out that even the presence of arteriosclerosis of the brain at the time of death did not prove the significance of arteriosclerosis for the genesis of a condition, the beginning of which may have occurred ten or fifteen years before death. Frequently one is surprised to see how little arteriosclerosis is present in the brain of patients with shaking palsy, although the general pathologist may have reported some sclerosis of the vessels of the body organs.

Our observations suggest that in some cases of "arteriosclerotic paralysis agitans" vascular changes in the brain have been mistaken for arteriosclerosis. It is worth while to notice that the perivascular calcification, which was seen in several instances in our material, occurred only in the globus pallidus, was located in the adventitia and consisted of ring calcification or deposits of calcium corpuscles in the perivascular spaces. The picture is entirely different from what is generally recognized as arteriosclerosis of the vessels. As early as 1894, Redlich was quite definite in his conclusions that those vascular changes which he observed in the spinal cord represented an endo- and periarteritic process and not "senile" changes. In our material, case 1 falls into the group of senile paralysis agitans which develops toward the end of the sixties. The brain showed generalized degenerative and gliotic alterations with vascular sclerosis.

Whatever these vascular changes are, there is no doubt that alterations of the vascular system form an impressive part of the pathology. It is of interest to mention that Vogt considered the "status disintegrationis" in connection with the formation of lacunae as so typical of paralysis agitans that he wrote "status disintegrationis or paralysis agitans." Although Ramsay Hunt felt that C and O Vogt have placed too great stress on the "état criblé" and "état precriblé" in the causation of paralysis agitans, many other investigators were impressed by the vascular changes. Bielchowsky (42) wrote that of decisive importance for the pathogenesis of paralysis agitans "are in my opinion the alterations of the vascular system and the destruction of the parenchyma depending upon them." McDonald Chrichtley (43) emphasized that the état criblé and the lacunae of cerebral disintegration are the best illustrations of the dissemination of small lesions with integrity of the intervening structures.

Wilson (44) has offered in his text book a chart demonstrating the frequency of paralysis agitans according to age.

AGE	PERCENTAGE
21-30	1.0
31-40	7.1
41-50	19.0
51-60	39.0
61-70	26.9
71-80	5.4

For the younger age groups mentioned by Wilson, one wonders how many cases would turn out to be of encephalitic origin if an autopsy study were available in the first years of development of the symptoms. Most pathologists who studied cases of paralysis agitans in the younger age group came to the conclusion that they were dealing with a post-encephalitic condition. The cases of Hunt and van Bogaert will be discussed later.

In our own material, the youngest case with no history of encephalitis died at the age of 49 (case 4). The peculiar findings in the cortex, globus pallidus, putamen and caudate nucleus which showed some round cell infiltration, perivascular calcium deposits, ependymitis and marginal gliosis were similar to changes seen in cases 5 and 6 and suggested encephalitis as a causative factor. One certainly would not consider this case as a merely degenerative process. The same is true for case 8 who died at the age of 60 but developed symptoms at the age of 50, and case 7 who developed symptoms at the age of 40. In case 2 the onset was reported at the age of 51. In these cases the alterations were compatible with inflammatory or toxic agents and there was no indication of a mere senile process, nor were the findings sufficient to justify the diagnosis of a heredo-degenerative, "abiotrophic" process.

Several observations, however, indicate that Parkinson's disease may develop without encephalitis and the conception that every case of Parkinson's disease represents a chronic encephalitis is not justified. Lundborg (45), in 1912, collected material of a Swedish family with myoclonus-epilepsy. There were 8 cases of chronic progressive paralysis agitans related to 17 patients with myoclonus-epilepsy, a percentage of paralysis agitans incidence which certainly deserves attention. In one branch of the family, paralysis agitans was found in the grandfather, father, and son.

Hart (46) found a hereditary factor in 16 per cent of his material of 219 cases. Collins and Muskies (47) also reported hereditary factors in paralysis agitans. In 1930 Ferdinand Kehrer (48) gave an elaborate review of the literature of familial incidence of paralysis agitans. Eleven authors have reported paralysis agitans in siblings. Medea and Clerice in 1898 observed paralysis agitans in 4 siblings of 10. Spiller, Jackson, and Immermann, in 1916 and 1919, reported the incidence of paralysis agitans in 4 brothers. Twenty-one authors reported paralysis agitans in several generations, the highest incidence reported in Runge's paper in 1924 with the disease present 7 times in father and son among 53 patients.

These observations are suggestive of hereditary factors and have led some authors to postulate a heredo-degenerative paralysis agitans. Unfortunately, there are no reliable post-mortem studies available of cases which had a definite history of familiar incidence and died in early life.

The conception of a juvenile paralysis agitans was introduced by Willige (49) in 1911. This author reported a case which developed at the age of 22, he gave a review of cases of juvenile paralysis agitans in the literature. These cases, however, were not studied well enough to render definite information. The same is unfortunately true with Ramsey-Hunt's (15) observation. He reported in

1917 a patient whose tremor of the left foot started at the age of 15. The tremor gradually increased and involved later the other side. At 23, tremor of face, tongue, and eyes, and general dysarthria were observed. Death occurred at the age of 40. The pathology was, in Hunt's opinion, confined to the corpus striatum where he found merely a degeneration of cells. Another case of that type which began at the age of 7 years with tremor of the left arm, extending later to the left leg, is reported by van Bogaert (50). At the age of 12 years the tremor involved the right side. Later the whole body shook. At autopsy pathology was found in the globus pallidus. In the caudate and putamen there were some alterations but little was found in the substantia nigra.

Although these 2 cases of juvenile paralysis agitans have attracted considerable attention, the cases were not well enough studied to stand criticism. This problem should be investigated further and only a thorough genetic, clinical and pathologic study of cases of juvenile Parkinson's disease will bring the solution of that question.

From observations on Wilson's disease, a close relationship between liver and striatum has been postulated (51). Recently reported observations on brains of children, who died several years after having erythroblastic anemia, have produced evidence of a striking bleaching of the globus pallidus, due to demyelination and fibre degeneration (52). One must, therefore, consider that toxic metabolic substances may involve the extra-pyramidal system and produce a precocious and selective degeneration.

Whether the localization of the lesions and their character are the only factors in producing the paralysis agitans syndrome or whether it may occur only in persons of a certain psychological type is a question which has attracted some attention. For an obviously motor disease it has produced a good many psychological speculations. As early as in 1910 at a meeting of the New York Neurological Society to which we have referred previously (9) the expression was used "The Parkinsonian is the reward of virtue." Camp mentioned in his lectures (53) that paralysis agitans "occurs more often in hard working, conscientious people, who do not drink, smoke, or take vacations." But these sentences come more from "general experience" than any special study.

Jelliffe (54) and recently Booth (55) have directed special attention to the personality of the Parkinsonian patient. Jelliffe, using psychoanalytic methods, studied some of their psychological attitudes and concluded that the personality was the main factor, while the brain lesions were of less importance. Booth (55), using the Rorschach and other psychiatric methods, felt also that men with a special type of personality were prone to develop paralysis agitans. An exhaustive psychiatric study of the personality of postencephalitic patients has been offered by Ives Hendrick (56). None of this data is extensive enough, nor sufficiently well controlled, to convince us that personality plays anything but a minor role in the development of paralysis agitans. No author has dwelled on the other problem why the many individuals with this special type of personality, do not develop paralysis agitans.

No one has yet succeeded in producing Parkinsonian tremor in laboratory

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4 It has taken much time and many controversies to establish the main pathology of Parkinson's disease. Proved facts seem to be (a) that the substantia nigra is almost invariably damaged, (b) that the lesions are widespread and not restricted to the substantia nigra, (c) the pyramidal system is spared.

5 Our material of eight cases offers evidence that the substantia nigra is one of the most common sites of lesions in paralysis agitans. Cases with unilateral tremor revealed marked differences in the destruction of the substantia nigra cells of the left and right side, the contralateral side being more involved, while the degeneration of the globus pallidus was of the same extent on both sides. In all cases with a complete histological examination, it was found that lesions were not restricted to the substantia nigra. The cortico-striatal connections were regularly involved and lesions of the frontal and precentral cortex were evident.

6 A discussion of the physiology and pathology of the extrapyramidal system is offered in order to clarify the nomenclature and to emphasize the differences in the pathology of the various extrapyramidal diseases.

7 An analysis of the Parkinsonian tremor reveals that the tremor is not a "resting" tremor, nor is the tremor a true hyperkinesia. The tremor is a part of the hypokinetic syndrome and seems to occur because those cortical impulses which are conveyed through the pyramidal tracts reach the endorgan, while the discharges conveyed through extrapyramidal pathways are out of order. Transmission of the motor nerve-impulses is thus reduced and simplified to the primitive pattern of synchronized innervation, alternating in antagonistic groups of muscles. Thus Parkinsonian tremor is due to a diffuse disorganization of the extrapyramidal motor mechanism causing a new configuration of the paths that remain capable of function.

8 Our cases, as well as the literature, indicate that a large number of cases which are called "idiopathic" are cases of inflammatory brain disease. Some of them are residuals of epidemic encephalitis but other types of encephalitis may produce the same syndrome. The production of paralysis agitans by syphilis has been reported and tumor and trauma are known to cause transient and atypical Parkinsonian syndromes.

9 It is established that paralysis agitans may develop because of arteriosclerotic changes of the brain but this etiology is not so common as one would expect from the literature. Even in cases where the pathologist reported arteriosclerotic changes in the other organs the arteriosclerotic alterations of the cerebral vessels are frequently negligible.

10 Senile tremor with some stiffness does not justify the diagnosis of paralysis agitans. As a matter of fact, senile changes in the brains of paralysis agitans patients are rare.

11 After discussing the various types of symptomatic paralysis agitans the question remains whether or not all cases ought to be considered as "symptomatic." Many investigators feel that there remains an original group of cases which represents a nosological entity. Genetic studies have suggested an "abiotrophic," heredo-degenerative group which develops in earlier life and represents a similar nosologic entity to Wilson's disease and Hunting-

animals. Small children do not display such tremors even though extrapyramidal disorders are frequent in childhood. These facts suggest that a certain degree of maturity and development of the brain is needed before the full-fledged picture of Parkinson's syndrome can occur. This cannot be used as an argument that a certain type of psychological integration is essential, although it may be that persons with a marked motor drive are most likely to develop the syndrome than those of a more sedentary type.

Therapy

It is not within the scope of this study to discuss therapy in detail.⁴ The treatment of paralysis agitans has been very conservative up to the last five years, being restricted to the use of scopolamine, stramonium and atropine preparations, mostly mixed. Recently saturation with atropine (57) and the Bulgarian belladonna (58) have attracted much attention. These methods seem to be somewhat more effective than the older ones (59).

During the last three years the surgical approach to the problem of extrapyramidal disorders has made great progress. Much has been learned from these operations, but the original enthusiasm over the preliminary reports is being severely dampened by careful follow-up work. So far, surgical treatment has been of several varieties: removal of cortical area 6 (39), partial removal of area 4 (60), severing the ansa lenticularis (40), and partial sectioning of the motor tracts of the spinal cord (61). The most impressive surgical successes are not achieved in cases of true, bilateral paralysis agitans, but in unilateral conditions of unusual type and varied etiology, such as trauma. Much more experience is needed before surgical treatment can be recommended for Parkinson's disease.

SUMMARY

1. At the time of the one hundred and twenty-fifth anniversary of James Parkinson's essay on shaking palsy, his masterful description is still unsurpassed.

2. Clinical investigations in Parkinson's disease have reiterated most of his observations and have explained the clinical picture of this disease as an extrapyramidal disorder. The main symptoms which have been added since Parkinson are the mask-like face, disorders of speech, cogwheel rigidity of the limbs, the fading out of handwriting and other motions, the slowness of reactions and numerous dysfunctions of the autonomic nervous system, such as the greasy skin. It is still a matter of argument whether these latter disorders are due to involvement of the hypothalamus or are part of the dysfunction caused by lesion of the substantia nigra which may play a part in autonomic as well as motor regulation.

3. The appearance of postencephalitic paralysis agitans has brought about unexpected insight into the complex pathology of the extrapyramidal motor disorders. It seems well established that the lower nuclei of the basal ganglia, especially the substantia nigra, are most involved in that condition.

⁴ Since writing this article, a comprehensive survey of the methods of treatment in postencephalitic Parkinson's disease by von Witzleben (63) has been published.

tricle The inferior olivary nucleus showed gliosis with pyknosis of the nerve cells The vessels of the brain showed enlargement of the lumen and marked enlargement of the perivascular spaces There was marked stasis in many areas No arteriosclerosis was present in the cerebral vessels

Case II (P B B H , A37/50) The patient, a sixty-one year old Jewish male, entered the hospital because of abdominal cramps for one week and abdominal distension for three days For the past ten years the patient has had Parkinsonian syndrome with a coarse tremor of both hands For the last several years he had dyspnea on exertion and swollen ankles The physical examination revealed a fairly well developed, elderly man with a coarse, shaking tremor of both hands, arms and legs His color was slightly cyanotic, respiration increased, blood pressure 180 to 120 Peripheral vessels showed definite evidence of sclerosis and tortuosity The reflexes were present and slightly hyperactive but no pathologic reflexes were found The abdomen of the patient was distended and an operation for volvulus by colostomy was performed The patient died ten days later

Autopsy The general examination was non-contributory The brain weighed 1365 grams, the vessels at the base showed only a few scattered atheromatous plaques Blocks were taken from various areas of the cortex, both basal ganglia, including the subthalamic region, brain stem, pons and medulla The spinal cord was not available for examination Microscopical examination of the brain revealed that the cerebral vessels were almost entirely free from arteriosclerosis The only severe vascular changes were found in a small section of the globus pallidus and here calcification occurred in the form of deposits in the adventitia, while media and intima were free from lesions Each substantia nigra showed severe loss of cells and demyelination of the neighboring fibres The subthalamic nucleus also showed degeneration of cells and severe demyelination In the wall of the third and fourth ventricles there were a few ependymal reactions in the form of ependymitis granulosa and multiplication of the ependymal layer In the region around the third ventricle some small hemorrhages were noticeable The globus pallidus showed very marked demyelination of its fibres, especially in the outer section of this nucleus, and some degeneration of the cells In the putamen, the perivascular spaces were enlarged and status lacunaris of a minor degree was recognizable The same type of changes was found in the cerebellum where the dentate nucleus showed demyelination and degeneration of cells The cerebellar cortex showed loss of the intraganglionic fibres and demyelination of the white core The Purkinje cells showed some sclerosis Sections from the cerebral cortex showed widespread loss of nerve cells, gliosis of the first layer, some atrophy and compensatory fibrosis of the leptomeninges and demyelination of the white core Especially marked was the loss of the myelinated radiation and the demyelination of the short association fibres The vascular spaces in the white core showed enlargement and perivascular scarring

Case III (P B B H , A37/97) This sixty year old retired salesman entered the hospital complaining of tremor of the left arm and weakness About one year ago, patient first noticed tremor of the left hand which occurred when the hand was at rest The tremor decreased on using the hand The tremor gradually increased in the following months and began to involve the elbow and the patient noticed weakness of the hand Eventually the tremor became so marked that it bothered him at night when he went to bed, but it did not bother him when he slept in a chair During the last three weeks before entry to the hospital, he noticed weakness of the feet Weakness was more marked on the left side, the left foot being hard to start walking but when started, patient had no difficulties in continuing to walk The physical examination revealed a well-developed, obese man of 205 pounds weight Left hand and forearm showed coarse tremor until stopped by holding the hand or placing the hand under his head The tremor disappeared on doing something purposeful with this hand The patient tended to hold his body slightly fixed, he walked with quick, short, shuffling steps His mental state was clear but the patient was slow in

ton's chorea Pathological studies have so far failed to establish such an entity The few reports are not worked up well enough to be conclusive This problem should be investigated further and only a thorough genetic, clinical and pathological study of cases of so-called juvenile paralysis agitans will bring about the solution of that question

12 The therapy of Parkinson's disease has been very conservative until lately when neurosurgery has opened a new approach by attacking the extrapyramidal system directly It remains to be seen how far this active treatment will be beneficial to the various types of paralysis agitans Our clinicopathological studies suggest that, taking into consideration the chronic inflammatory character of many cases and the possibility of toxic agents in other cases, it is conceivable that a more ingenious medical approach to the disease may succeed in developing a more hopeful therapy

APPENDIX

Case Reports

Case I (P B B H , A36/24) The patient was a seventy-one year old male when he entered the Surgical Service of the P B B H complaining of weakness, nocturia, dysuria, dribbling and progressive retention which became more severe during the last ten days prior to admission He was previously employed as a railroad worker In March of 1934 he was on the Medical Service complaining of generalized weakness and tremor of hands, progressively increasing for two years Physical examination at that time showed a poorly nourished man with fixed expression, dry, scaly skin, coarse tremor of hands, more on left, inability to supinate the left arm except with prolonged effort, generalized increased myotonia with some cog-wheel rigidity, peripheral arteriosclerosis Stramonium was prescribed without relief He showed, however some improvement under hyoscine bromide

In December 1935 he entered the hospital again with difficulties in urination Since last discharge he had grown gradually weaker and had had increased difficulty in executing coordinated movements The physical examination at the second admission showed an emaciated, apparently quiet man with fixed gaze and coarse tremor of the left arm and hand On speaking, the tremor was exaggerated and similar movements appeared involving the head and right arm He had pill-rolling movements of the left hand and the reflexes were slightly more active on the left side but no pathological reflexes were present The recent difficulties in urination were due to a symmetrically enlarged prostate Suprapubic cystotomy was performed and a week later he began to have diarrhoea which he continued to have until his death about two weeks after operation

Autopsy The body length measured 165 cm Generalized arteriosclerosis and arcus senilis were present The brain weighed 1490 grams Blocks were cut for microscopic examination from various parts of the cortex, from both basal ganglia, from the brain stem and the medulla The spinal cord was not available for examination

Sections through the frontal cortex showed an enormous increase in oligodendroglia, microglia and a slight increase in astrocytes The white matter showed some demyelination The first layer of the cortex was thinned out In spite of the gliosis, most ganglion cells were rather well preserved and little loss of ganglion cells was recognizable Under high power the cells appeared in different states of dissolution In the basal ganglia large and small lacunae were noticeable The nerve cells showed slight signs of degeneration but most of the cells were relatively well preserved The substantia nigra showed a high degree of degeneration with dissolution of the cells and scattered pigment There was a tremendous increase in glia throughout the section, involving not only the substantia nigra but the substantia reticularis and the central gray around the aqueduct and fourth ven-

to vomit and had involuntary evacuation of bladder and rectum. The temperature rose to 108.4° by axilla, pulse to 140 and respirations were gasping and terminal in character. In spite of stimulation, the patient died one hour later of acute pyrexia. Discharge diagnosis: post-encephalitic Parkinsonism, pedunculated fibroid, heat stroke.

Autopsy. In the peritoneal cavity multiple pedunculated leiomyomas attached to the fundus of the uterus were discovered. One large intramural leiomyoma 5 cm. in diameter and six irregular pedunculated masses ranging in size from 2 to 10 cm. in diameter were found. The heart weighed 240 grams. There were many sub-endoocardial hemorrhages in the left ventricle, most marked in the region below the aortic valve.

The brain weighed 1240 grams. There was a moderate increase in subarachnoid fluid, meningeal vessels congested, vessels at the base normal, very slight flattening of convolutions. Serial frontal sections revealed no gross pathological changes with the exception of slight congestion of capillaries throughout the parenchyma. Fluid in the ventricles was clear and slightly blood-tinged. Cerebellum and brain stem were grossly normal.

Microscopic examination of the brain revealed the brain free from arteriosclerotic changes but the same ring calcification encountered in other cases was marked in sections of the globus pallidus. There was perivascular enlargement of the small and medium-sized vessels not restricted to any particular area. A study of the right and left basal ganglia revealed patchy lesions which seem to depend upon the vascular system (status lacunaris). There was slight glia reaction around the vessels and formation of a myelinated plaque in the right putamen. The fibers of the globus pallidus showed marked demyelination with balloon formation of the remaining myelin sheaths. There was marked satellitosis and some degeneration of nerve cells. No essential difference between the right and left sides was recognizable. It might be that on the right side there were quantitatively a few more lesions. Sections from the cerebral cortex revealed marked loss of cells, atrophy with fibrotic thickening of the leptomeninges (frontal), marked satellitosis of the nerve cells and patchy demyelination of the white core.

Case I. In this case (already briefly reported by one of us (22)) the history of encephalitis four and a half years before death was definite. The patient was a chauffeur, aged forty-two at the time of his death. At thirty-seven he had encephalitis with acute symptoms for several weeks, then there gradually developed a rigidity which interfered considerably with his walking and eating. Little by little he became more and more helpless until finally, when he was hospitalized, he was a perfect picture of Parkinson's syndrome, with rigidity, tremor and movement of the trunk and limbs en bloc. He also showed interesting sympathetic symptoms: ruddy face, marked seborrhea and conspicuous increase of salivary secretion. Three years after the onset of the disease he became completely bed-ridden and lay rigid without spontaneous movement. He died four and a half years after the onset.

Autopsy. Examination showed unusual vascular changes. The lesions may be summarized as follows:

Cerebral cortex. Marked vascular changes throughout with increase in number and size of vessels. Great congestion, vessel walls either thin or thickened, hyaline and sclerotic. Hemorrhages in the white matter of both motor areas with iron deposit in hemorrhages and about nearby vessels. Adjacent cellular destruction ascribable to ischemia, also chronic inflammatory changes in frontal and parietal cortex not immediately affected by hemorrhages, slight leptomeningitis, slight marginal gliosis, marked perivascular gliosis, "Mucin-like" bodies and abundant "amyloid" bodies and intermediate stages.

Basal ganglia. On right and left marked chronic cellular degeneration is found throughout, especially of the pallidal cells, more acute changes in putamen, necrotic areas near sclerotic blood vessels especially in the pallidum. Abundant amyloid bodies. Numerous and congested blood vessels some with thickened and hyaline walls, some thrombosed vessels others contracted and empty. No hemorrhages. Rings of iron deposited in adventitia of vessel walls of part of the right pallidum. Perivascular and diffuse gliosis.

answering questions or in initiating any action. The reflexes were normal, the face expressionless, the gait shuffling, both legs showed varicositas of veins. Sudden death occurred on the fifteenth hospital day. The case was apparently one of paralysis agitans complicated by generalized vascular disease, chronic glomerular nephritis, the terminal and deciding factor being pulmonary infarction and associated pleurisy.

Autopsy The body length measured 170 cms. General examination showed that the patient died of pulmonary infarction and bilateral bronchopneumonia. There were generalized arteriosclerosis, cardiac hypertrophy and pulmonary emboli. The brain weighed 1380 grams. Microscopic examination of the brain showed ependymitis over the caudate nucleus and a multiplication of the ependymal cells in other areas. There was some subependymal gliosis. In both globi pallidi there was marked enlargement of the blood vessels and their perivascular spaces with rarefaction and softening of the surrounding tissue. There was a definite demyelination in each globus pallidus. The perivascular spaces were frequently found filled with gutter cells. Enlargement of the perivascular spaces and degeneration of the surrounding tissues were present in the putamen and caudate nucleus. In the caudate nuclei there was some capillary sclerosis and marked increase in glia, while the alterations were of a less degree in the putamen. No arteriosclerosis was found. In a few areas of the pallidum and in the knee of the capsula interna, the vessels were surrounded by a heavy ring of dark blue staining "calcified material." This deposit did not involve the media, but was outside and within the adventitia. The fibres of the capsula interna were found intact. The sections through the subthalamic region showed demyelination of the fibres of the ansa lenticularis on their way around the medial border of the capsula interna. On the whole, the cells of the basal ganglia and the subthalamic region were well preserved, while the demyelination of the globus pallidus fibres was marked. Most outstanding were the changes in the substantia nigra. It showed definite loss of cells in the lateral areas of both sides, but the right side was more affected, it being only two-thirds the size of the left. The fibres showed definite demyelination. In the cortex loss of ganglion cells and thinning out of the first layer with scattered areas of softening were found all over. Within the very large perivascular spaces there were found many red blood cells and some small hemorrhages in the pons and the region around the third ventricle.

Case IV (C.H., A37/403) The patient, a white female of 49 years entered the hospital with complaints about shaking of left leg, weakness and drooling. The patient noticed the weakness of her leg and the onset of drooling about one year before admission. During this period the drooling became worse. She developed rigidity, weakness and marked tremors of the left leg and foot. She did not notice tremors of the hands. About one month before entry she developed polyphagia, polyuria and polydipsia, but no pruritus. In an Out-Patient examination two weeks before admission sugar in the urine was discovered. There was no history obtainable of encephalitis, no history of diplopia or dizziness. The physical examination disclosed a well-developed and moderately well-nourished female with mask-like typical facies. Pupils were equal, regular and reacted to light and accommodation. The heart appeared slightly enlarged with a basal and aortic systolic murmur, rapid and regular. The neurological examination disclosed inability to move facial muscles, marked tremors of legs and a slight tremor of the left hand. There was cogwheel rigidity of the left leg. No abnormal reflexes elicited. The diagnosis was 1. Diabetes mellitus, 2. Parkinsonism, 3. post-encephalitis (?), 4. abdominal mass, calcified fibroid (?). The X-ray examination showed a hypertrophic arthritis of the lumbo-sacral spine. The urine was essentially negative in the hospital, hemoglobin 81%, blood sugar 87%; Hinton negative. At admission the patient had a temperature of 99.4° displaying characteristic signs of post-encephalitic Parkinsonism. She also had an abdominal tumor which was thought to be a pedunculated fibroid. On admission the patient was placed on stramonium. On the ward the patient had very few complaints and ran an uneventful course until four days later when her temperature rose to 100° and the pulse to 120. On the next day, the temperature was 101°, pulse 110. That night the patient suddenly began

movements were very slowly performed and after a brief time had to be stopped. When stimulated, he tried to start but stopped again and his motion faded out. The gait was very peculiar. The right leg was stiffer than the left and when he walked he moved the leg with a jerking motion. The leg revealed a coarse tremor which could be stopped for a short time but recurred when the patient's attention was fatigued and increased in intensity with increasing fatigue. The arms and legs showed cogwheel rigidity. The reflexes were exaggerated but no clonus, Babinski or Oppenheim were present. The tongue showed fine fibrillation. There was excessive salivation. His mental behavior during the examination showed many peculiarities. He understood commands and attempted sometimes to perform them but after a short time he was unable to keep on. Sometimes he would arise spontaneously from his chair and run around in circles continuing to do so until he was interrupted. Before sitting down he would turn around sometimes three or four times. These circles were almost always counter clockwise. He was able to run quickly but his normal gait was stiff and slow.

The clinical picture strongly suggested a postencephalitic parkinsonism, but the history is not complete enough to ascertain whether or not the child had encephalitis at the age of seven months. The development of this child seemed to have passed through two stages, the first, which occurred before puberty, is that of restlessness, lack of inhibition and vicious character trends. After puberty the picture changed entirely into a picture of parkinsonism. The boy died at the age of 18½ years of pneumonia.

Autopsy. The circumference of the head measured 53.8 cms. The brain weighed 1320 grams.¹ The dura was strictly adherent to the calvarium. On gross inspection the brain appeared normal.

If one expected to find overwhelming lesions explaining such a striking clinical picture, one would be disappointed, because only a very careful microscopical examination revealed the pathological changes. More than five hundred slides were made and stained by various methods. The spinal cord, medulla and pons showed almost no lesions with the exception of one level where a small focus was found in the substantia reticularis of the pons, the lesion consisted of a pile of lymphocytes near a vein which showed perivascular cuffing. The nerve cells of the spinal cord and medulla appeared well preserved at the different levels. The central canal in the spinal cord showed complete obliteration and a somewhat unusual proliferation of the ependymal cells. Obvious pathological changes were found in the substantia nigra, the pigmented cells were almost completely destroyed and the field was covered with small glia cells. The veins of the midbrain showed definite cuffing with small dark stained round cells, while the arteries appeared almost free. There was some microglia reaction on the side of the brain tissue. The destruction of the substantia nigra cells was in contrast to the good preservation of the nuclei of the pons. In the diencephalon round cell cuffing was found in many veins of the putamen, globus pallidus and the subthalamic region. In some areas the perivascular tissue was loaded with concretions which stained dark blue with myelin stains. In hematoxylin and eosin preparations these areas appeared necrotic, colorless or of a faint brownish-green tint. In elastica van Gieson's stain, those areas were filled with a fine mesh-work of red connective tissue fibres. In the tannic acid silver method, this mesh-work stained dark brown. In the putamen, there were few nerve cells recognizable and the ground substance appeared darker in myelin preparations than usually. The ansa lenticularis was in some areas interrupted due to perivascular necrosis.

The most marked lesions of the white matter were in the frontal and precentral areas where the perivascular tissue contained great accumulations of the same dark blue concrement. The perivascular spaces were enlarged and the white matter showed demyelina-

¹ Both measurements indicate that the mental retardation was probably due to accidental factors and not to a primary mental deficiency. The period of constant crying occurred in May 1921 when there was a large number of cases of encephalitis lethargica in Sweden, the birthplace of our patient.

The most interesting study in these specimens is that of the sections colored with Pearl's iron stain. In the pallidum are found many blood vessels with dark blue rings of iron in the vessel walls. These are for the most part the vessels mentioned as having hyaline walls, but a study of the distribution of these iron-ringed vessels shows that they are restricted to the pallidum and for the most part to the inner segment. The hyaline-walled vessels, on the other hand, are found throughout the rhombencephalon and to a less extent in all parts of the brain. A close inspection of these iron-ringed vessels shows that the ferruginous deposit lies in the adventitial layer of the vessel wall, and largely in the newly added adventitia—the thickening of the vessel wall probably resulting from inflammation in the perivascular space. In some cases the iron ring is narrow and lies in a thin layer of connective tissue. In other cases, in which the Virchow-Robin space is distended with organized exudate, the iron makes a broad band. Many vessels have hyaline degeneration outside of the thickened adventitia. It is thus seen that the iron lies in the connective tissue beneath the hyaline and outside the media of the vessel wall.

Midbrain. Bilateral depigmentation and degeneration of substantia nigra. Extensive vascular lesions like those described in the basal ganglia. Cellular destruction in the left oculomotor nucleus. Chronic ependymitis.

Cerebellum. Degeneration of cells in the dentate nucleus, subacute and chronic vascular lesions nearby, surrounded by necrosis. Myelin degeneration in the superior peduncles. Vascular lesions in the pontile tracts and nuclei, and one inferior peduncle.

Medulla oblongata. Perivascular lymphocytosis in somewhat wide Virchow-Robin spaces, chronic sclerotic changes in the vessel walls with surrounding necrosis of tissue, especially near the inferior olivary nuclei.

Spinal cord. Diffuse peripheral myelin degeneration, thick-walled blood vessels with some perivascular infiltration, chronic leptomeningitis.

Dorsal roots and ganglia. Chronic pericellular fibrosis.

Muscle. Chronic atrophy and fibrosis.

Skin. Local hypertrophy of sebaceous glands.

Case VI (W S S, A38/35). The patient was an eighteen year old boy in whom a complete picture of paralysis agitans developed under our own observations. He was previously a strong and healthy looking boy of Swedish extraction who was mentally retarded from early childhood, but whose physical development appeared normal. When he was seven months old he cried continually, but according to a statement made by the mother, the doctor in Sweden told her this was nothing serious. He walked at the age of sixteen months and talked at two years. When he was seven years old, the mother began to notice slowness in development. Because of his mental retardation, he was admitted to an institution.

At the time of admission, he appeared physically well developed and well nourished. His station was normal and his gait somewhat hesitating, but otherwise normal, reflexes normal, no tremors. The boy was very noisy and exceedingly active. He proved to be vicious toward other children and sometimes deliberately pushed them down or bit them. He was a difficult child to control, and it was almost impossible to get his attention for any length of time. At the age of nine, another peculiarity was observed, he had a tendency to run around in circles, and, when asked to go straight ahead, he would suddenly turn around and proceed running in circles. Up to the age of seventeen there were few changes noted in his physical development. He grew to be a tall, strong and healthy looking boy.

A neurological examination at the age of seventeen revealed a peculiar posture which suggested Parkinson's syndrome, at first sight. He appeared stiff and his movements were slow and poor. His head was bent forward and saliva was dropping from his mouth in a constant stream. The right arm was slightly bent and rigid and did not move when he walked. The hand was stiff and showed marked coarse tremor. He did not use the right arm spontaneously and rigidity was so marked that he was not able to touch his face with his right hand. The left arm was more flexible and the patient made some use of this arm. He was able to lift the arm to his face to scratch himself and he tried to tie his shoes. These

Putamen and caudate nucleus The cells stained rather poorly, but numerous ganglion cells were recognizable and comparison with the cells of the insula did not reveal much difference in staining reaction. The fibres showed some demyelination in several sections of the putamen, and status criblé. The vessels showed hypertrophy and multiplication of the intima with proliferation of the adventitia. The fibre connections of the subthalamic region showed some demyelination especially of the ansa lenticularis. The cells of the substantia innominata were rather well preserved but some patchy destruction was recognizable due to criblé formation of the tissue.

The cells of the thalamus were well preserved. Also the lower parts of the basal ganglion did not show alterations.

The midbrain Serial sections through the midbrain showed that the substantia nigra had completely disappeared on the left side at higher levels. In the lower levels there was to be noted a slight degree of alterations in the cells, but the difference between both sides was not striking.

Medulla oblongata Sections through the oblongata at the largest development of the nucleus olivarius demonstrate marked glia-fiber-proliferation. The cells of the nucleus olivarius were shrunken and thorn-apple-like. The cells of the nucleus ventralis and dorsalis of the vagus showed partial degeneration and fat stains revealed that most of the cells were possibly more than usually degenerated.

Cortex Sections through different parts showed congestion of the cortex and demyelination of the white matter around the fibres. The perivascular spaces were large and parts of the cortex showed status criblé of the same extent as seen in the putamen. In one convolution "plaque-fibro-mélinéque" was discovered. The pia arachnoid showed patchy thickening upon some convolutions of the frontal and precentral areas.

Spinal cord Examination of the spinal cord at the different levels revealed many changes of the anterior horn cells. The number of cells was reduced, many of the remaining ones showed chromatolysis. The capillaries showed some capillary sclerosis.

Case VIII (#7380 M.G.H.) Only a brief record was available. Since childhood the patient was a backward member of society and while having the advantage of special tutors, he was never able to go through the usual course of education which was enjoyed by other members of his family. During the last years he had been subject to attacks of unconsciousness accompanied by convulsions and followed by a period of somnolence. In a typical attack the patient was found lying stretched out in bed, head and eyes turned to the right, frothing at the mouth, right leg spasmodically jerking, the left arm and leg stiff. This was followed by a jerking of the right arm and twitching of the right side of the face. His pulse was irregular, but of normal rate as before the attack. The blood pressure was 190 to 105, his previous blood pressure having been about 140 to 95. Following the attack the tongue appeared to protrude somewhat to the left. The left grasp was greater than the right. The arm reflexes were equal and active.

The patient developed a rhythmic tremor especially of the left arm, hand and head. There was cog-wheel rigidity of the left arm and wrist. Following his last attack of unconsciousness on July 8, 1934, he was somnolent for three days. He was short of breath, his chest showed increased signs of passive congestion and his temperature rose to a height of 103 degrees. He died July 16, 1934. The diagnosis was made of "Hemi-Parkinson" and convulsive seizures. Age at the time of death, about sixty years.

Autopsy. The body was that of a well-developed and moderately well nourished male weighing approximately 160 lbs. From the autopsy findings we might note the more important observations. The heart was moderately enlarged and weighed 400 gms. The descending coronary artery branch at the left was found markedly calcified and upon section complete occlusion was disclosed with a grayish white hard concentric thrombus. There was no evidence of fresh occlusion. In the aorta, near the junction of the arch and descending thoracic aorta, an unusual type of aneurysm was found. The aneurysm involved approximately one-half the circumference of the aorta measuring 4 cm. in width, 1.5 cm. in depth and 1.5 cm. in height. The lining of the aneurysm was smooth throughout except

tion around the veins The exterior walls of the veins appeared covered with a thin layer of small round cells The gray matter of the cortex showed patchy degeneration and patches of inflammation with thinning out of the first layer and sclerogyrria Although this pathological process was present in all areas, the frontal and the precentral areas appeared especially involved

Case VII (M G H #7063) The patient came in 1933 at the age of sixty-three years to the Out Patient Department of the Massachusetts General Hospital for the first time In 1909 at the age of thirty-nine, he developed severe pain above the nose and later in and above the right eye The pain was accompanied by a whirling vertigo which made him stagger to the left He never fell The legs became progressively weaker He lost strength and control of the right arm In 1933 the patient could not write with his right hand, the fingers "had no life," and he could not feel things as well as with the left hand The patient said that when the pain came he saw double He could not button clothes with the right hand, which was weak and clumsy No real headache or vomiting No deafness or speech defects

Neurological examination The pupils did not react to light or distance The fundi vessels were somewhat tortuous and sclerotic He did not look to the left or upward with the right eye The 5th, 7th, 8th, 9th and 10th nerves appeared normal Handwriting showed marked tremor and incoordination The patient did not seem able to use his right hand, he held it stiffly and could not use it to dress himself Extreme rigidity was found on attempting passive motions The right leg was stiff and showed tremor Abdominal reflexes were absent, Hoffmann's sign was present bilaterally The clinical impression was that the patient had hysteria but the diplopia seemed to rule that out, probably the diagnosis was extrapyramidal disease

The X-ray findings were notable Marked convolutional prominence and the vascular channels in the frontal region were quite prominent, especially of the frontal bone just above the right frontal sinus There was also slight increase in the density of the bone around this area, the Crista Galli appeared to be absent The sella turcica was deep and the posterior clinoids were atrophic There were no areas of calcification within the skull The pineal was not definitely visualized X-ray findings were definitely abnormal Variations from the normal and the absence of Crista Galli, diminished vascular channels in the right frontal bone, increased convolutional markings together with atrophy of the posterior clinoids, were definite X-ray evidence of increased intracranial pressure

Hinton and Wassermann were negative

The patient was admitted, August 14, 1933, for pulmonary tuberculosis and Parkinson's disease The history mentioned for two years, weakness and atrophy of the right arm, difficulty in writing and tremor For about one year right leg has been stiff and he has had diplopia on looking to the left

At the end of August the patient took a definite turn for the worse He was well oriented, answered questions, but his reactions were very slow He seemed to stop and think for one-half to two minutes before answering and sometimes repeated the questions Memory was poor

Neurological findings Ptosis of the right eye The left eye was considerably more prominent Pupils were round, equal and reacted fairly well to light Could not test accommodation Patient would not look up, down, or to the left Looked only to the right There was cog-wheel rigidity of all four extremities In the right arm there the cog-wheel rigidity was especially strong

The patient died of advanced tuberculosis on September 22, 1933

Autopsy The brain showed macroscopically an enlargement of both ventricles, especially of the left There was a slight general atrophy of the brain

Microscopic examination Our first interest dealt with the corpus striatum The basal ganglia were cut in serial sections and examined by various methods

Globus pallidus The ganglion cells were (at least in several areas) well preserved The fibres showed some demyelination especially near the putamen

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for one small atheromatous ulceration 7 mm in diameter. The brain weighed 1100 gms. There was moderate arteriosclerosis, the wall of the main arteries being cloudy but fairly well collapsed without well marked atheromatous plaques. The convolutions of both parietal lobes appeared to be smaller than normal but the crowns were rounded and the fissures were not unusually wide. The appearance was suggestive of congenitally narrow convolutions rather than atrophy. No depressions suggestive of localized degeneration were observed on the surface of either hemisphere and there was no difference in the two hemispheres in size, shape or consistency.

Macroscopically, the brain showed definite atrophy especially of the left frontal lobe. In the right temporal lobe a dark area measuring 2 cms in length was found beneath the cortex which turned out to be a venous angioma. Microscopical examination revealed gliosis of the nucleus olivarius inferior. There was proliferation of the glia fibres, and the ganglion cells showed fatty degeneration. There was also fatty degeneration of cells of the 10th, 11th, and 12th nuclei. The margin of the medulla showed abundant marginal gliosis as well as the gray matter around the fourth ventricle. Sections through the midbrain showed patchy degeneration of the substantia nigra especially on the left side. The degeneration was more of an insular character in this case than in the last one, and in some areas the cells were rather well preserved. There was a gliosis of the griseum centrale and the velum medullare.

On sections through the subthalamic nucleus and the ansa lenticularis widespread status cribre was recognizable. The vessels of the substantia-perforata were enlarged and partially thrombosed with perivascular infiltration of round cells. In the substantia innominata many areas were found necrotic. The ansa lenticularis showed some degeneration near its medial end with enlarged vascular spaces.

On sections through the lentiform nucleus and the insula, large areas of rarefaction were recognizable in the putamen and in the white matter of the insula. The fibres of the capsula interna and claustrum were demyelinated. The cell degeneration in the insula cortex was more marked than that of the putamen. Degeneration of cells, however, was widespread in the pallidum, caudate nucleus and putamen. The cerebral cortex, especially the frontal, showed patchy degeneration, marginal gliosis and focal thickening of the meninges. The white matter showed marked demyelination.

A very peculiar finding occurred in the right temporal lobe. The white matter appeared perforated and showed enormous increase in enlarged veins. The tissue between the vessels was degenerated and in many sections the walls of the veins touched each other. One of the bigger central vessels appeared thrombosed. The proper term for this condition is probably venous angioma simplex or cavernoma. The thrombo-phlebitis which was recognizable in some vessels seemed to be a secondary infection.

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THE ECOLOGY OF PLAGUE*

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I INTRODUCTION

An analysis of the present factual knowledge of plague appears timely, since the discovery of the disease in recent years as sylvatic plague or plague of the wild rodents in the inland states of the North American Continent has attracted much attention and has created considerable anxiety. The discoveries of apparently new areas harboring squirrels infected with the plague bacillus should be looked upon as an important domestic problem subject to slow but careful investigation, but for reasons by no means clearly understood rat plague has re-appeared in a Western port subject to restrictions imposed by the International Sanitary Conventions, and consequently the whole problem has become acute. As a cause of death, plague plays a subordinate rôle. During the past 10 years only 17 cases have been definitely recognized. However it is feared that the wild rodent reservoirs so widely scattered over 12 Western States and Canada may ultimately extend into the rat infested cities and towns of the Mississippi Valley, or in turn it may re-invade the Pacific Coast cities and visit military encampments, and thus bring again the fearsome seed close to the human habitations. Nobody anticipates that bubonic plague will cause epidemics of the same magnitude as it did 300 years ago. But since so little of the ecology of the wild rodents is known, the behavior of this disease cannot be forecast. Likewise, as a self-regulating phenomenon in which man is merely an accidental host to a broad rodent parasitism in his environment, it should be capable of description. In attempting such a description, it is fully realized that the epidemiology of the wild rodent disease—the effect of the plague bacillus on the rodent herd—is far more important than the data on human cases. That the records concerning the statistics and the dynamics of these primary hosts together with their fauna of ectoparasites in the United States are quite incomplete will become apparent in the course of the narrative. It is therefore only proper to weave into the synthesis the significant but rarely read contributions by the students of sylvatic plague in South Africa and Russia. A historical account may well serve as an introduction to the substance of the lecture.

II HISTORICAL REVIEW OF PLAGUE IN THE WESTERN STATES

Bubonic plague was first recognized in the United States at San Francisco. On March 6, 1900, through the vigilance of Police Surgeon Dr. Frank P. Wilson,

* De Lamar Lecture delivered at the Johns Hopkins University School of Hygiene and Public Health

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eradication that had been concentrated in 9 counties. During 1914, plague was found only in 4 counties, or more accurately on 21 ranches. At the time the pronunciamiento was made, these ranches had been thoroughly poisoned and hunted over from 3 to 5 times, with the result that only on 1 ranch was a plague squirrel found after the work was recorded as completed. The author of the cheerful statement "danger of its further spread has been removed" should not be criticized. Little was known at that time concerning the periodic-cyclic fluctuations of sylvatic plague in an everlasting succession. The health official, who is little versed in these matters, should be especially judicious in the prognostications of epizootic trends of wild rodents.

Since the finding of infected rats in Seattle and New Orleans in 1912 and 1914, with the appearance of human plague in the latter city in 1914 (30 cases with 10 deaths), and in 1920 and 1921 (25 cases with 11 deaths), as well as the infections in Florida and Texas, have no immediate relationship to the problems of today, it is deemed unnecessary to recite the details. Although the official records continued to list plague-infected squirrels in the regions surrounding the Bay area, no human infections were recognized. A feeling of security and optimism prevailed, and was continuously reflected in the official statements, when, with thunderbolt-like swiftness, 13 cases of rapidly fatal pneumonic plague occurred in Oakland between August 15 and September 11, 1919. The circumstances of the catastrophe, which involved 2 doctors and 2 nurses, were epidemiologically interpreted by Force and Kelly (see W. B. Kellogg)². They came to the conclusion that the first patient, an Italian, who developed a secondary plague pneumonia following the opening of a bubo in the right axilla, had hunted and shot squirrels in the foothills of Alameda county on August 11 and 13, 1919, bringing them home where they were prepared for eating. The entire outbreak was traced again to the squirrel plague reservoir.

The 6 human bubonic plague cases with 5 deaths, which were seen between 1920 and 1923, invariably took place in County areas where squirrel infection was readily demonstrable by the customary method of investigation. In brief, the method consisted of shooting the squirrels in the field, packing the carcasses in milk cans and sending them to the laboratory where they were submitted to a careful postmortem examination for the purpose of detecting evidence of cross-plague infection. When one realizes that over 8,000 squirrels, sometimes decomposed, were examined from one county before any infection was discovered, it is indeed not surprising to note occasional disappointments and surprises in the discovery of new foci in areas remote from the original epizootic.

An outbreak of plague described by Dickie for Los Angeles in 1924 with 41 recorded cases, 33 of the pneumonic type with 31 deaths, and 8 of the bubonic type with 3 deaths was associated with a simultaneous recognition of rat plague.³ The first case was a Mexican woman who maintained a rooming or

² Am J Pub Health, 1920, 10, 599

³ An intensive campaign for the eradication of rats and ground squirrels was undertaken in both the city and rural districts. The trapping of 110,167 rats conducted during 7 months following the outbreak yielded 199 or 0.18 per cent positive for plague. However, at the same time 16,094 squirrels were examined and 9 were proven infected with *P. pestis*.

tember, 1910, not less than 150,000 squirrels and proven 402 or 0.26 per cent infected. Not less than 10 Counties harbored diseased rodents. In fact, it is very important to note that late in 1910 a diseased *Citellus* was found as far South as San Miguel in San Luis Obispo County, a distance of at least 200 miles from the supposed portal of entry at the Sacramento River near Port Costa where, according to Dr. Medros, a rodent epizootic made its appearance at the waterfront in 1903. Likewise, it was recognized at various places (Gustine and Los Banos) in the San Joaquin Valley. In consequence, it was not surprising that the area of human infection extended into the rural sections of the state,

TABLE 1

Hunting Operations and Ground Squirrel Infection in California, 1908-1920, according to Different Official Records

YEAR	(1) W. M. DICKIE PLAGUE IN CALIFORNIA 1900-1925			(2) ANNUAL REPORT SURGEON GENERAL UNITED STATES PUBLIC HEALTH FOR 1916			(3) J. D. LONG PLAGUE ERADICATION IN CALIFORNIA		
	Number examined	Number infected	Percent- age	Number examined	Number infected	Percent- age	Number examined	Number infected	Percent age
1908	—	4	—						
1909	3,826	42	1.10						
1910	113,655	354	0.31						
1911	124,265	55	0.04						
1912	56,703	613	1.08	19,335	506	2.61	29,144	902	(0.3%) 3.05
1913	30,408	680	2.2	16,186	283	1.74	22,464	419	1.86
1914	18,322	177	0.96	13,162	44	0.34	18,722	417	2.17
1915	29,057	39	0.13	15,594	10	0.05	22,990	69	0.3
1916	63,598	138	0.22	44,751	83	0.18			
1917	4,174	43	1.03						
1918	9,772	22	0.23						
1919*	72,021	124	0.17						
1920*	45,892	185	0.4						

(1) Proceedings of the Conference of State and Provincial Health Authorities of North America, 1926

(2) Page 259

(3) Public Health Reports, 1913, 28:2470, Public Health Reports, 1914, 29:3105

* Corrected data

and by 1915 at least 24 cases with 15 deaths were directly attributed to exposure to squirrels in San Benito, San Joaquin, Stanislaus and Santa Clara, in addition to the originally recognized foci in Contra Costa and Alameda counties. As will be discussed later, these rural human plague infections were associated with localized rodent epizootics which appeared despite the intensive eradication measures continuously in progress, the apparent success of which is evidenced by the numerical reduction in proven infected wild rodents (Table 1).

By 1914, a predication was ventured that all "discoverable" plague had been eradicated from the State of California. The occasion for this optimism was the apparently complete suppression of plague as the result of the squirrel

the total yearly population in the state in July at approximately 30,000 000 ground squirrels, one would have to reckon with an average of 15 000 plague-infected rodents, some concentrated on a few acres and others scattered widely over many counties. Indeed, this fear-inspiring estimate assumes an aspect of reality when one studies the destructive progress of a local epizootic.

In June 1927, the California State Department of Public Health assumed the organization and maintenance of a small force of hunters for the purpose of making plague surveys in counties bordering the coast line. Instead of sending the carcasses of the shot squirrels to the laboratory where they frequently arrived in an advanced state of decomposition, the rodents are now dissected and carefully examined in the field. Pathological lesions are noted, specimens are taken and placed in glass containers which are shipped in ice-packed metal shipping boxes to the laboratory for examination. The extent of squirrel plague in various California counties between 1927 and 1933 is in part reflected by the number of infected rodents which were discovered. In Table 2 the yearly number of rodents shot and the number of squirrels found infected are listed.

The figures fail to give a true picture of the dynamic intensity of sylvatic plague in certain counties or in certain narrow sections or ranches of these counties since the survey activities in search for extensions of the regional epizootics or for undiscovered areas by necessity add to the grand total a great many animals from non-infected places. Thus the yearly figures merely suggest that in 1927 to 1930 rodent plague was more common than in subsequent years. When the records for certain counties are inspected one notes, for example, that in Contra Costa in 1927-1928 in 2,360 squirrels 46 or 1.9 per cent were diseased. It is therefore not surprising that a fatal case of bubonic plague was observed in that county. The years 1928 and 1929 were doubtless "plague years" and the three human infections in Monterey, Santa Barbara and Santa Cruz Counties resulted from local rodent epizootics. For example in Monterey 11 infected squirrels were found in 626 squirrels or 1.7 per cent, while in Santa Cruz 556 rodents furnished 45 or 5.2 per cent plague-infected animals. Nevertheless it must be remembered that the first human case in Santa Barbara County in September, 1928 was not associated with any marked rodent mortality. In fact, the careful examination of 1,273 squirrels was entirely negative. A year later 2 diseased squirrels were found on the ranch where the case had occurred. Personal inquiries and observations made during 1927-1928 showed that epizootics were rampant in Santa Clara and Santa Cruz Counties. At that time the question of recrudescence or fresh importation was raised but it was quite apparent that plague infection was still rather widely disseminated among the ground squirrels in localities where infection in these rodents had previously been determined. Finally it is well to emphasize that all the plague areas were

* While mentioning these figures it may be recalled that in the fiscal year 1913-1914 approximately 20 150 000 squirrels were destroyed in the course of the control measures which were concentrated on 3,100,000 acres. A great many areas since then recognized as enzootic plague districts were not included in this attempt to destroy completely the squirrel and insure the elimination of the disease (Long).

boarding house. She died after an illness of 4 days. Her husband and a practical nurse, who had attended her, were taken ill shortly afterward and died. The cause of death was given as lobular pneumonia. A few days following these deaths, it was reported that a number of Mexicans living in this district were severely ill. The ambulance driver who removed cases to the hospital, the priest who administered the last rites, nurses at the hospital and contact with these patients developed the disease in rapid sequence. Relatives of patients in outlying districts, who had been contacts, also developed pneumonic plague. In considering the ultimate origin of the rodent infection, two possibilities were carefully studied: (1) the introduction of the infection from foreign ports through San Pedro, the port of Los Angeles, and (2) the transfer of plague from infected ground squirrels to rats. The first possibility was dismissed, since intensive trapping operations in San Pedro disclosed no plague-diseased rats. Early consideration was therefore given to the second possibility of transmission of the infection to rats from ground squirrels. Contact between these two rodents existed in many sections of the city, and infected squirrels were found in the urban sections not only in 1924 and 1925 but it is recalled as early as 1908. In an examination of 699 rats with 2,685 fleas (average per rat 3.8) it was found that 64 or 2.4 per cent of the insects were squirrel fleas. Although the intensive shooting survey operations between 1908 and 1915 revealed no anatomically infected squirrels, there is no proof to the contrary that Los Angeles County had not been an endemic center for many years preceding the epidemic of 1924.

One fact is frequently overlooked: that an old plague focus on the L. Ranch in San Luis Obispo County, with a marked rodent mortality in 1907 and 1908 became active again and a definite epizootic described as a violent outbreak or "virulent" epidemic, was reported in July, 1924. At least 8 squirrels collected at random and several others found dead as a result of poisoning proved to be plague-infected. Officially, these epizootics were considered "further extensions of the disease in squirrels," when in reality they were more readily comparable with the periodic local epizootics, which are known to occur in many species of rodents. Indeed, it is therefore not surprising that simultaneously with the episodes in the two southern counties, active epizootics of squirrel plague were also noted in the North (San Benito, Monterey, in sections of Contra Costa and Santa Clara Counties). Truly, 1924 was a sylvatic plague year in California, with its consequences on the human population.

Summarizing its work on plague and the suppressive measures employed in California for the period 1908-1927, the United States Public Health Service (see Report of Surgeon General, 1927) reports the examination of approximately 558,706 squirrels with 2,069 proven plague infections. Thus, an animal survey catch of 30,000 rodents should produce, if the disease is spread uniformly over the endemic area and occurs yearly with the same intensity, an average of 15 plague-infected animals. The statistics previously presented show that in typical plague years this figure has, as a rule, been many times greater. Furthermore, if one estimates, according to Joseph Grinnell and Joseph Dixon,

had never been observed as far South as the San Bernardino Mountains, and furthermore for several years rodents had been killed in these areas in connection with relapsing fever studies. No reports concerning epizootics in this region were obtainable and certainly no rodents with lesions suggestive of plague passed over the dissecting tables. However, while these discussions were in progress, the survey crew of hunters pursued a report that an increased mortality among ground squirrels was in progress in the Lynn Valley in Kern County in the foothills of the Sierra Nevada. Although during July and September 1933 squirrels were killed, the cause of the mortality was not determined. From previous experiences, this epizootic had all the characteristics of sylvatic plague. It was then realized and so recommended, that an examination of the ectoparasite—the flea—for plague bacilli, as already used by Pirie on wild rodents and by Ogata on rats, might supply valuable information. A limited series of fleas were inoculated into guinea pigs with negative results. Since the collecting of fleas is time-consuming and the crew had to make urgent surveys, this method of search for obscure plague foci was not put into official practice until 1936.

There is weighty evidence in the form of clinical histories and positive serologic agglutination tests which would place in June, 1933, three cases of *pestis minor* in children living outside of Fresno in some relationship to the events in the lower San Joaquin Valley. The following year, end of March, 1934, on the ranches adjacent to the Lynn Valley, a gigantic rodent epizootic, proven to be caused by *P. pestis*, rolled over an area of close to 970 square miles in Kern and 300 square miles in Tulare County. For the first time in the history of sylvatic plague in California an opportunity was afforded to study the progress of an *epizootic*. The country involved is typical, saddle-like in character. Gently rolling hills almost barren of vegetation and with no visible water, have a top made of lime-laden formation dotted with bizarre masses of rocks. The latter were honeycombed with square burrows in which skulls or pelts and remains of skeletons or masses of fur or maggots amply attested to the progress of mass mortalities undergone. With little effort, no less than 2551 carcasses were collected. All stages of a plague infection from the acute septicaemic to the chronic form with marked pulmonary involvement and profuse plague bacilli in sputum were noted. Due to hot weather, the carcasses rapidly decomposed. Most and rodents, some with large masses of submaxillary lymph nodes suggestive of those on some *S. gambelii* were picked up. Over hills are bordered on one of the flanks *attested* by the many carcasses of young animals. By the middle of June some carcasses were completely freed from *S. gambelii* but others were between two *S. gambelii* and *S. gambelii* of *S. gambelii* densely populated on sides of *S. gambelii* were present. In some yards the infestation amounted to 200 to 400 to the acre, and in one case of a *S. gambelii* infestation a density of 600 to 700 to the acre. It is not for rats that the fleas were collected but for ground squirrels and *S. gambelii* of the country. In the light of the above, not more than half a dozen *S. gambelii* and *S. gambelii* of the country were collected. The *S. gambelii* were apparently completely exterminated in the

demonstrated in the coast counties or districts adjacent to these counties, extending from the Carquinez Straits of the Sacramento River to Los Angeles

That the low infection index in 1931 and 1932 by no means represented the potential extent of the infection smoldering in California and other Western territories was amply proven by the experiences gathered during the subsequent 8 years. The facts which led to the discovery of a much larger reservoir of infection are not generally known. A brief account therefore appears ap-

TABLE 2

Ground Squirrel Infection in California, 1927-1941

Obtained through the courtesy of Mr E T Ross, California State Department of Public Health

YEAR	NUMBER EXAMINED	NUMBER INFECTED	PER CENT	HUMAN INFECTIONS
1927	10,446	39	0.37	1+
1928	5,403	59	6.1	3 (2+)
1929	14,888	105	0.7	
1930	9,742	12	0.13	
1931	16,948	14	0.08	
1932	13,654	8	0.05	
1933	30,950	10	0.03	4 (1+)
1934	26,851	258	0.92	1 (1+)
1935	27,880	116	0.30	—
1936	23,377	136	0.58	4
		(7 pools of fleas)		
1937	30,660	4	[0.01]	1 (1+)
		(11 pools of rodents)		
		(32 pools of fleas)		
1938	18,713	7	[0.069]	—
		(6 pools of rodents)		
		(17 pools of fleas)		
1939	29,232	5	[0.02]	—
		(1 pool of rodents)		
		(5 pools of fleas)		
1940	28,381	1	[0.007]	—
		(1 pool of rodents)		
		(5 pools of fleas)		
1941 (August)	19,040	17	[0.1]	2 (2+)
		(3 pools of rodents)		
		(61 pools of fleas)		
		(1 pool of ticks)		

propriate. While considering the source of infection of a fatal case of bubonic plague in a town outside of Los Angeles, three possibilities suggested themselves (1) local rodents in the vicinity of the town, (2) Los Angeles City and (3) a summer resort in the San Bernardino Mountains. Since no evidence of plague in the two first listed areas could be demonstrated and since the incubation time strongly favored the sojourn in a mountain cabin, inductively the third possibility was accepted as the most likely. However, it was argued that plague

is a common rodent disease the investigators have never detected the disease in squirrels. However the hunting dragnet engaged to find plague-infected squirrels will annually bring to the laboratory 2 to 4 animals with lesions and cultural findings of tularemia. But, in recent years every true epizootic among various species of squirrels was invariably proven to be caused by *P. pestis*. Since sylvatic plague tenaciously persists in its original haunts it is reasonable to conclude in retrospect that previous wild rodent epizootics in Modoc County and elsewhere in the Western states were in all probability, not tularemia but plague.

Shortly after the discovery of sylvatic plague in Northern California reports were received of a fatal case of human bubonic plague at Lake View, Oregon (May 1934). Surveys and the demonstration of infected Oregon and Columbia squirrels by the United States Public Health Service showed that the Southern Oregonian plague area responsible for this human infection was connected with the California plague region and that this part of Modoc had become invaded from the North. Of interest is the fact that an epizootic of marmots near the men's camp in the Hart Mountain was in progress before the infection in the squirrels was detected. During 1935 it progressively infiltrated the recesses of the Warner Mountains and spread in a southerly direction into Lassen County. The Valley meadows yielded dead (19S) and infected Oregon squirrels (71 per cent of 1492 shot) wood rats (*Neotoma*) and white-footed field mice (*Peromyscus*). In April 1935 shortly after the first squirrels emerged from hibernation the survey activities were undertaken and on April 30 on one ranch still in part covered with snow, 62 carcasses were found and in a sample of 101 adult squirrels 6 showed subacute lesions of plague. Inquiries made in Oregon left no doubt that according to dependable reports squirrel epizootics occurred in Telocasset in 1927 and 1928 and in the Sumpter Valley in 1928 and 1929, or at the time the old plague areas were quite active in California.

The rise of sylvatic plague in the United States was ushered in by the demonstration of plague by the Public Health Service in a Richardson ground squirrel (*Citellus richardsoni*) near Dillon, Montana in 1935 and in *Citellus amabilis* in Idaho with the first human bubonic plague infection in Southern Utah. In rapid succession each year since 1934 has brought new surprises. Four non-fatal human cases of plague were proven in California in 1936. A veterinarian living in a county where plague was unknown developed an axillary plague bubo. He had treated a cat with an abscessed jaw but no proof could be secured to incriminate the carnivore as a possible source of infection. Stray infective fleas brought to the animal hospital on dogs were likewise suspected. The recreational areas around Lake Tahoe and Big Bear in the San Bernardino Mountains with their varied fauna of chipmunks and golden mantled squirrels yielded few diseased rodents but pools of fleas collected from the healthy animals proved to carry the *P. pestis* when tested on guinea pigs. The great value of this procedure employed in the search for endemic plague foci in densely wooded areas was realized by those who had to deal with the epidemiological investigations of human infections in areas generally considered free from disease. For

During the field investigations 82 carcasses of squirrels found dead in the main areas of the epizootic in Kern County were sent to the laboratory, plague bacilli were isolated from the heart blood, the spleen or lung lesions of 75. Similarly 66 of 78 dead rodents found in Tulare County were definitely proven infected. In a series of 2,831 animals shot by the survey crew, 27 had acute or resolving lesions of plague with positive findings. At the end of the survey operations, the sample of squirrels collected at random and secured through the hunting operations yielded 70, or 11 per cent, proven infected squirrels. Pertinent to an understanding of the factors which conditioned this regional epizootic is the fact that it started in adult squirrels early in March shortly after the rutting season, it extended to the young the latter part of May and early June, and that it evolved in regions in which no rodent control work had been practiced during the depression years from 1930 onward. This huge reservoir was responsible for one human bubonic plague infection in a boy who died from a secondary chronic meningeal localization of the plague bacillus on the 121st day after the onset of his illness.

Needless to say, the plague situation appeared critical. For the first time, the disease had "migrated," or probably it is more correct to say it was recognized on the east side of the San Joaquin Valley in the foothills of the Sierra Nevada without leaving markings concerning its wanderings, though it was quite apparent that the trails pointed to mountains and not the lowlands. The evolution of these new plague areas on a gigantic scale, despite suppressive measures, created justifiable concern. Discussions incident to these unforeseen developments acquainted the representatives of the various agricultural and biological survey agencies with the problems involved. It is not surprising that about the first of June a United States Biological Survey crew engaged in distributing poison on Government land in Modoc County—the most northeasterly county of the state—reported dying and dead squirrels on several ranches. Surveys made during the summer proved plague in 51 per cent of the shot or dead Oregon ground squirrels [*Citellus oregonus* (Merriam)] collected in an area of approximately 65,000 acres. Significant was the apparent mortality among wood rats (*Neotoma* sp.), however, only one carcass suitable for bacteriologic examinations was obtained. Again, it was reliably reported that at periodic intervals over many years, even before 1900, squirrels had died in these regions. Old timers claimed the disappearance of the rodents in the early nineties. Since tularemia is by no means uncommon in this particular part of California, it was quite generally believed, in view of certain misinterpretations of published facts and lack of interest in the diseases of the animal kingdom, that the wild rodent epizootics were caused by *Bacterium tularense*. Investigations and inquiries have disclosed the important fact that, even in the presence of an extensive epizootic of tularemia among rabbits and hares, associated and conditioned by an undue prevalence of *Haemaphysalis leporis*—the rabbit tick—only an occasional squirrel is similarly diseased. According to R. G. Green, in the Lake Alexander area in Minnesota where tree squirrels and Franklin squirrels [*Citellus Franklini* (Sabine)] are present in numbers and tularemia

assume that the rodent infection has not been confined to California alone. In this connection it may be rather disturbing to be reminded of the historical facts concerning tularemia. First seen in Arizona in 1907 and then described as a disease of squirrels from California in 1910, its nation-wide distribution was only recognized in the years 1924 to 1928 when physicians had learned to diagnose a disease which existed for years in their immediate vicinity. Somewhat the same course of events led to the recognition of typhus, spotted fever and brucellosis. There is every reason to predict that annually in widely separated sections of the western part of the United States sporadic cases of bubonic plague may make their appearance. From the historical records, it is axiomatic that human cases served as indicators or signal posts of existing wild rodent enzootics or epizootics. For the most part at least in recent years visible outbreaks have occurred at a time when the density of squirrel populations has reached a peak in numbers and is being reduced by an epizootic. It is however a peculiar fact that human cases rarely if ever occur in the midst of the outbreaks. Only too often a cursory survey may fail to yield diseased rodents but produce a few pools of infected fleas. Why human cases are so sporadic remains a mystery. There must be some inherent unknown weakness in the link formed by the flea which is responsible for the very infrequent occurrence of the human cases. This view has likewise been expressed by Fourie in considering the situation as it exists today in South Africa. This sporadicity of bubonic plague in parts of the country where it has never been identified and seldom seen makes it understandable why the diagnosis of human plague is frequently missed and is only made after recovery or death. From personal experience during the past 10 years at least 12 of the 17 cases reported fall into the category of mistaken diagnoses.

How the majority of the 50 bubonic human plague cases dealing with 41 males and only 9 females, contracted their infection is not discernible from the records nor has it been possible to get any clear conception relative to the pathways of the infective agent. In the early histories one finds statements concerning the hunting and skinning of squirrels from epizootic areas. That, in boys and girls, a bite from a *Citellus* or chipmunk may lead to an axillary bubo was recognized in at least six instances. The handling and burying of dead rodents scratches or other wounds sustained in handling predators, or picking of magpie nests (*Pica pica hudsonica*) have been associated with infections. Twenty-four of the cases were under 20 years of age. In 17 cases the location of the primary bubo was in the inguinal region while in only 12 of the detailed reports was the axillary node involved. The latter may or may not have been induced by an infective insect bite indeed there is some evidence in the histories as already indicated that they may be due to direct traumatic contact. Unfortunately it will always remain a matter of conjecture as to the actual number of cases which were caused by insect bites, since primary skin ulcers have been reported in but 2 cases. However the frequent location of the primary process in the inguinal region which was not always identified as a bubo strongly incriminates flea-bites on the limbs. Probably some have become

example, the customary dissection of shot rodents between 1931 and 1936 in the San Bernardino Mountains had failed completely to disclose the existence of plague until 2 pools of 104 fleas from 38 Fisher squirrels and 31 insects from 24 squirrels, respectively, were proven plague-infected. Incident to the human infections in Utah, sylvatic plague was demonstrated for the first time in the marmot (*Marmota flaviventris englehardti*) and prairie dogs (*Cynomys parvidens*). New foci of plague were found in Idaho, Montana and Nevada and old endemic areas in California revealed renewed and occasionally epizootic activity to such an extent that, for example, in Santa Cruz the disease incidence in the squirrel catches reached the significant percentage of 8. Infected fleas were encountered in increasing numbers in the pools of the collected ectoparasites.

The plague season of 1937 was ushered in by a human bubonic plague case with a typical primary ulcer at the site of the flea-bite. It occurred on the Nevada side of Lake Tahoe. In August, it was followed by a fatal infection in a girl having been bitten by a chipmunk, while on a vacation at Huntington Lake in Fresno County. The survey studies conducted on a scale hitherto unknown in the annals of sylvatic plague on the American continent covered every Western state, and diligently pursued every report on local rodent mortalities. Ample evidence promptly confirmed the ever growing suspicion and fear that the disease is prevalent in the North from the International Boundary, in Washington, to the California San Bernardino Mountain Range in the South, and from the West Coast of California into the heart of Montana. The boundaries were subsequently extended in 1938 and 1939 into Catron County of New Mexico, and into Arizona and Wyoming. By 1940 it was recognized in Alberta, Canada, and this year (1941) in North Dakota. Finally, Colorado, through the survey of an epizootic in San Miguel County, was placed among the 13 Western states now proven infected. New hosts of the plague bacillus, such as the Kangaroo rat and the Washington cotton-tail rabbit, and lately the supposedly immune Douglas squirrel, were added to the already lengthy list of rodents suffering from spontaneous plague. Despite these endemic reservoirs, only the active epizootic areas in Idaho in 1940 and in Siskiyou County in California in 1941 resulted in one and two, respectively, fatal septicemic or bubonic human plague infections.

III THE PRESENT SITUATION

The present situation may be summarized thus. Plague is enzootic in the rodent population over at least 12 Western states of the Union and at least in 1 province in Canada. Human cases of plague, reflecting the minimum area of the distribution of plague in the wild rodents, have been recognized during the past 39 years in California (45 bubonic + 13 pneumonic types, total 58), Idaho (1), Nevada (1), Oregon (1) and Utah (2) (total 63). Only during the past 6 years, for the first time, infected rodents have been proved in states other than California. It is probable, however, that the infection has existed in these Commonwealths for a long period of years. For the reason that plague has persisted in the wild rodents of California for more than 36 years, it is reasonable to

tered in tissue sections or aspirated exudates from human lymph nodes Both in culture and in guinea pig inoculation tests of these strains, they reverted to the classical type Their infectiousness and cultural characteristics were in no way different from other strains

Approximately 80 strains tested for their fermentative characteristics reacted in dextrose, levulose, galactose, mannite and maltose but not in glycerine Hence, the plague strains connected with North American human and rodent infections belong to the glycerine-negative, Beta group (Kuraichi), also known as the "Oceanic Race" according to the designation of Berlin and Borzenkov These races or types are encountered in the endemic belt of islands and peninsulas of the Tropics They differ from the "Continental Race" or "Alpha Type" which ferment glycerine, and are found in an endemic belt throughout the Central Asiatic Plateau These facts have been used by Kuraichi to speculate on the origin of plague in California Since the pandemic starting from Hongkong in 1894 was associated with the "Oceanic Race," he believes that ample evidence is available to consider the North American enzootic foci to be descendants of this race He overlooks the fact that Pirie in South Africa found in a collection of 23 plague strains 4 of the "Continental Race" The African sylvatic plague endemic focus is likewise attributed to the pandemic dispersion at the turn of the century Thus, it appears inadvisable to use biochemical tests to support certain theories concerning the origin of plague on the North American Continent

Simple agglutination tests with formalin treated antigens have proven most useful to identify quickly the different strains of *P. pestis*, there are differences in the agglutinability of different strains, but no conclusive evidence of any definite grouping within the species is as yet available from the preliminary tests Tests for the invasiveness and virulence of the California plague strains on guinea pigs and, in particular, on mice by the method of S. S. Sokhey have revealed only minor variations, which occurred as a result of dosage or varying susceptibility of the animals Considerable time has been devoted by several workers to prove pneumotropic properties for the bacilli isolated in Oakland and in the Los Angeles outbreaks, or from a diversity of wild rodents It was recognized in conformity with the findings of other investigators that, except on direct respiratory infection, the degree of lung involvement in the test animals depends more on the length of illness than upon anything else In fact, since the susceptibility of the test animal par excellence, the guinea pig, is doubtless different from that of man, the difficult pneumonic plague problem will not be solved by further studies of the plague bacillus supposedly endowed with a specific lung "virulence" developed on passage through rodents of ground squirrel and "ground-hog" type The rise of plague pneumonic epidemics depends on a great many varied factors, both of an intrinsic as well as an extrinsic nature Different chains of circumstances mold the nature of the epidemic and not the tropism of the causative agent

The ecological studies on the rodent reservoir were started by Wherry and McCoy relatively early as compared, for example, with the investigations in South Africa and Russia In 1908-1909 the existence of a possible reservoir of

so infected in the open country, but such cases are rare. The most usual place, where the infection has been contracted, has been the domestic premises in the rural communities, or the cottages and cabins of summer resorts. Agricultural laborers and their children of white, Portuguese and Japanese ancestry, in one instance a soldier who camped on a badly infected ranch, and in another, a sheepherder who attended to his profession on the forest meadows in the midst of a marmot epizootic, were the victims of plague. With the elimination of rat plague since 1925, exposure to wild rodents is more definitely evident and proven. In the early California cases, contact with domestic rats has not been ruled out to the complete satisfaction of every epidemiologist. If one excludes from consideration the cases of pneumonic plague which are always of a grave character and well-nigh hopeless, explosive in their epidemiologic character, and invariably due to aerogenic or mucous membrane to mucous membrane transfer of the plague bacillus, the case mortality rate of approximately 50 per cent for the bubonic, carbuncular and multiglandular cases due to wild rodents corresponds well with the averages for white persons recorded from recent epidemics observed in other sections of the World.

Up till 8 years ago, the diseased Beechey's squirrel—*Citellus beecheyi*—was ultimately the main source of infection. Lately, in 2 cases, chipmunks (*Eutamias*), in another the Say's rock squirrel (*Citellus variegatus grammurus*), in still others the marmot (*Marmota flaviventris nosophora*), the Fisher's ground squirrel (*Citellus beecheyi fisheri*) and the Douglas's ground squirrel (*Citellus douglasii*) are suspected as the prime spenders of infection to man. It has become evident, in conjunction with the extensive survey studies all over the West, that not less than 31 species of wild rodents form a reservoir of plague independent of the domestic rat, thus making the situation potentially more dangerous than in the past, and further adding complications to a situation which already in 1908 appeared formidable in all its ramifications.

The problem is thus clearly an ecological one, depending for its ultimate solution on a complete understanding of the interrelations between the plague bacillus, the rodent and flea population and factors of the environment. An analysis of the interaction of these components should give a picture of the course of events leading to man's infection.

IV FACTS DERIVED FROM PAST AND PRESENT INVESTIGATIONS

The strains of *P. pestis*—isolated as early as 1908 by McCoy from diseased squirrels and since then collected in connection with the survey studies and diagnoses of human infections—are biologically identical with the organisms secured from rats or other rodents in various parts of the World. No essential differences have been found, if they occurred, they were of such an order as is generally accepted within the species. At least with the methods available today, it is impossible to distinguish biologically a plague bacillus isolated from a wild rodent from that obtained from a rat. In this respect, the conclusions of McCoy have been fully confirmed in recent years. The pleomorphism has occasionally been confusing, in particular the "coccal" type so frequently encoun-

the former a Pasteurellosis and the latter a Listerellosis. On the American Continent such infections have not as yet been encountered, but there is no reason why these and possibly other infections, concurrently with or independently of plague, may not affect the rodent population. Unfortunately, the plague investigations even in California, are largely survey studies planned and executed to locate speedily the existence and extent of *P. pestis* infection. Certain excellent improvements in technique as for example, the use of pooled tissues and of ectoparasites have made possible a rapid progress. But ultimately in the interest of a better understanding of the problem, intensive field studies must replace the far-flung but rather cursory sampling of rodent population groups and the minutiae of laboratory investigations into finer details of plague bacteriology.

With this in mind, the Hooper Foundation with its staff of 2 mammalogists (F. C. Evans and R. Holdenried) and 2 entomologists (C. M. Wheeler and J. R. Douglas) assisted by the Department of Vertebrate Zoology (E. R. Hall and J. M. Linsdale) and Division of Zoology (T. I. Storer) and Entomology (M. A. Stewart), College of Agriculture, has initiated in a very modest way field studies to work out standard quantitative methods of collecting data, and of observations on rodents and fleas at a station near Bass Lake (5,000 feet altitude), Madera County, at Calaveras Dam, Alameda County, and on a ranch in Kern County. More recently, these studies are being supplemented by observations in an experimental enclosure. In what follows, reference will be made to these studies.

(a) *Rodent Population Studies*. To date, the exploratory surveys or the more detailed investigations of epizootic or enzootic plague areas in the western part of the United States have established spontaneous infections or reservoirs in a total of 31 rodents and rabbits as listed below in Table 3.

As primary hosts, the *Citellus* varieties are doubtless most important in the Pacific and Rocky Mountain States. On the other hand, in the Rocky Mountains from Wyoming to Arizona to the Great Plains the rôle of the prairie dogs (*Cynomys*) constitutes according to C. R. Eskey and V. H. Haas a definite and independent reservoir of plague. The position of the marmots in the canyon-riven sage plains of the Northern Great Basin as a permanent independent reservoir is not established. Likewise the rôle of the chipmunks (*Eutamias*), flying squirrels (*Glaucomys*) and California chickarees (*Tamiasciurus*) in the Sierra Nevada as primary hosts is not clear. Equally uncertain is the significance of the wood rats (*Neotoma*), white-footed mice (*Peromyscus*), kangaroo rats (*Dipodomys ordii ordii*) and the cotton-tail rabbits (*Sylvilagus nuttallii*) in the infection spectrum of sylvatic plague. They may become infected by virtue of their contact with infected squirrels or they may become important supplementary, secondary but potential ancillary hosts, and thus unrecognized and unsuspected disseminators of the plague bacillus. As a whole, the host relationship on the North American Continent is just as involved and differs in no way from that proven for South Africa, Southeast Russia and other sylvatic plague regions where the infection remains localized since a particular fauna maintains the

plague in the wild rodent population was realized, and through intensive studies by the United States Public Health Service in California overwhelmingly proven. Largely influenced by these activities but independently, the mammalogists under the leadership of Grinnell and Dixon collected valuable data on the ecology of the ground squirrel native to the State. It is only in the last 6 years that the potential proportions of the reservoir have been understood, but even today there are few facts which correlate the natural history of the rodent with the plague bacillus. In a general way the host-parasite relationship or the parasitology of the plague infection has been elucidated by McCoy and his associates, who saw dissections of thousands of rodents and the lesions of natural plague in at least 2,000 squirrels. They established the now well known fact that the gross anatomical changes, indicative of an infection, resemble more closely those found in the guinea pig than those present in the rats and mice. A bubo with a purulent focus in the inguinal region is noted in about four-fifths of all cases of squirrels, which have been shot in the course of hunting survey activities of fields and forests. In the acute stages, the spleen is invariably very much enlarged and quite dark, while in the subacute form caseation or purulent lesions, rich in *P. pestis*, in one or more of the internal organs—liver, spleen and lungs—are noted. Towards the end of an epizootic period or in an enzootic area, rodents with one lymph node containing small abscesses and very few bacilli are encountered. This form of infection is known as the residual type, and may be looked upon as cases which are in a state of recovery.

In recent years, K F Meyer has encountered in California in three separate regions, involving three separate species of squirrels (*Citellus beecheyi oregonus*, *Glaucomys sabrinus lascivus* and *Citellus beecheyi douglasii*), in the fall or shortly before hibernation and invariably at the end of an epizootic, few individual rodents which had been shot. The cadavers presented a general enlargement of the lymph nodes, but macroscopically or microscopically visible purulent lesions. Cultures yielded no plague bacilli, but the inoculation of the pulped tissues into guinea pigs have produced in six instances typical plague infections. This type of plague-infected squirrel without visible lesions is best designated as "latent" plague or a form of carrier condition, which may be one piece of evidence towards a better understanding of the problem of the persistence of plague among rodents between epizootics. Concerning the frequency of this stage of infection, no accurate data are as yet available, but inoculations of guinea pigs with the pooled spleens and lymph nodes of several series of rodents without visible lesions would strongly indicate a much wider distribution than was formerly anticipated. Pirie has encountered this form of infection once in a *Namagua gerbill*e and one Karoo rat, while the Russian workers (Grikurov, Tumanski and others) have seen it quite frequently, in fact, they claim to have developed serologic and cutaneous tests to detect the existence of carriers.

The early studies have likewise established in squirrels the existence of a plague-like disease, which was subsequently designated as tularemia. Probably other natural infections among indigenous rodents occur, in the light of the South African experiences with the so-called "de Aar" or "Tiger River" disease,

infective agent. A principal species belonging to the family *Sciuridae* or *Gerbillinae* living in subterranean colonies in families or singly presides over the exchanges of the plague bacillus while a group of small rodents (varieties of *Muridae* and *Jaculidae*) and rarely representatives of the *Leporidae* act as complementary and intermediate hosts by supporting the epidemicity and perhaps the dispersion of animal plague. These complex interplays deserve careful attention but they will only be understood when the ecology of the individual components involved is more definitely established.

The comparative susceptibility to plague of the species of wild rodents has been tested on a relatively few species in fact, not even those which are of common occurrence in any part of the plague-infected areas have been so examined. McCoy and McCoy and Smith and Meyer and Eddie established the disposition of the chipmunk, white-tailed antelope squirrel (*Citellus leucurus*), wood rat rock squirrel Arizona prairie dog, golden mantled squirrel, Oregon squirrel pocket rat and marmot long before these rodents were discovered spontaneously diseased in the Western States. Various *Microtus* and *Peromyscus* species of mice collected in plague regions have been subjected to artificial infection and proven quite susceptible to *P. pestis* applied through skin scarifications. There is not a very big range in their susceptibility although as a rule, the chipmunks golden mantled squirrels and field mice had the shortest survival time of $2\frac{1}{2}$ to 3 days. In a series of 10 Oregon squirrels with a survival time of $\frac{1}{2}$ to 10 days 1 survived, and of 5 marmots with periods of survival of from 8 to 10 days 2 remained alive and showed no lesions when autopsied on the 25th day after scarification. Since it was realized that in all probability, every rodent accepts the plague bacillus, it appeared of greater importance to determine the comparative susceptibility of the species of squirrels most frequently involved in California.

By injecting intracutaneously varying doses of plague bacilli into approximately 450 squirrels, consisting of *Citellus beecheyi fisheri* from Madera County—where sylvatic plague had not been demonstrated—and of *Citellus beecheyi beecheyi* from Alameda County known as a plague focus since 1916, it was noted that these two squirrel populations are composed of very susceptible as well as quite resistant individuals. The latter predominate in the region where plague has been proven. Sixty-three per cent of the rodents survive an injection of from 1 000 to 30 000 plague bacilli while only 40 per cent of the Fisheri squirrels from the non-plague area resist a like infection. Furthermore the tests confirm the epidemiologic fact that the susceptibility of the young immature rodents and habitability of the mature males to *P. pestis* infection is much higher than that of mature females. The cause and duration of this resistance are not satisfactorily explained. Although it is argued that the proven resistance of the rodents is largely due to a process of natural selection and survival of the resistant individuals the possibility of an immunity induced by a previous attack of the disease should not be entirely dismissed. The lesser susceptibility of a given rodent group strongly suggests that plague may have existed there in the past that it may be a factor in the disappearance of plague in a locality, and that it may furthermore offer an explanation for the gaps of continuity and

TABLE 3

*Wild Rodents and Rabbits of the Western States Found Plague-Infected**Order Rodentia**Family Sciuridae**Genus Citellus*, Ground squirrels

- 1 *Citellus armatus*, Uinta ground squirrel (E 1935)
- 2 *Citellus beecheyi beecheyi*, California ground squirrel [Wherry 1908 (>2500)]
- 3 *Citellus beecheyi douglasii*, Douglas ground squirrel (K F M 1941)
- 4 *Citellus beecheyi fisheri*, Fisher's ground squirrel (K F M 1937)
- 5 *Citellus beldingi oregonus*, Oregon ground squirrel (K F M 1934)
- 6 *Citellus columbianus columbianus*, Columbian ground squirrel (E 1938)
- 7 *Citellus columbianus ruficaudus*, Blue Mountain ground squirrel (E 1938)
- 8 *Citellus lateralis chrysodeirus*, Golden mantled ground squirrel (K F M 1937)
- 9 *Citellus richardsoni elegans*, Wyoming ground squirrel (E 1937)
- 10 *Citellus richardsoni nevadensis*, Nevada ground squirrel (E 1937)
- 11 *Citellus richardsoni richardsoni*, Richardson's ground squirrel (E 1935)
- 12 *Citellus variegatus grammurus*, Say's rock squirrel (E 1936)
- 13 *Citellus variegatus utah*, Utah rock squirrel (E 1936)
- 14 *Citellus washingtoni loringi*, Loring's ground squirrel (E 1938)
- 15 *Citellus washingtoni washingtoni*, Washington ground squirrel (E 1938)

Genus Tamiasciurus, Red squirrels

- 16 *Tamiasciurus douglasii albolimbatus*, California chickaree (K F M 1937)

Genus Glaucomys, Flying squirrels

- 17 *Glaucomys sabrinus luscivus*, Sierra flying squirrel (K F M 1937)

Genus Eutamias, Western chipmunks

- 18 *Eutamias quadrivittatus frater*, Tahoe chipmunk (E 1936)

Genus Cynomys, Prairie dogs

- 19 *Cynomys gunnisoni zuniensis*, Zuni prairie dog (E 1938)
- 20 *Cynomys leucurus*, White-tailed prairie dog (E 1938)
- 21 *Cynomys parvidens*, Utah prairie dog (E 1936)

Genus Marmota, Marmots

- 22 *Marmota flaviventris engelhardti*, Engelhardt marmot (E 1936)
- 23 *Marmota flaviventris nosophora*, Golden mantled marmot (E 1937)

Family Cricetidae, Native rats and mice*Genus Neotoma*, Wood rats

- 24 *Neotoma cinerea occidentalis*, Western bushy-tailed wood rat (K F M 1934)
- 25 *Neotoma fuscipes mohavensis*, Mohave desert wood rat (K F M 1934)
- 26 *Neotoma lepida intermedia*, Rhoad's wood rat (K F M 1934)
- 27 *Neotoma lepida lepida*, Desert wood rat (K F M 1935)

Genus Peromyscus, White-footed mice

- 28 *Peromyscus truei gilberti*, Gilbert's white-footed mouse (K F M 1934)
- 29 *Peromyscus truei truei*, True's white-footed mouse (K F M 1934)

Family Heteromyidae, Kangaroo rats and pocket mice*Genus Dipodomys*, Kangaroo rats

- 30 *Dipodomys ordii ordii*, Ord's kangaroo rat (E 1939)

Order Lagomorpha, Hares and rabbits*Family Leporidae*, Hares and rabbits*Genus Sylvilagus*, Cotton-tails

- 31 *Sylvilagus nuttalli nuttalli*, Washington cotton-tail (E 1939)

* Proven by Eskey (E) or Meyer (K F M)

The third type known as the 'colonial burrow' is largely used as a safety zone which may be from 100 to 200 feet in length, and forms a communicating system of underground runways connecting from 6 to 20 entrances or surface openings. The depth of this burrow system rarely goes below 40 inches; it is often inhabited by species of animals other than the rightful owners, such as ground owls, toads, gophers, rattlesnakes, scorpions, centipedes and mole-cricket. Comfortable nests made of grass blades, roots and fine stems of foxtail and needle grass are placed well back in the burrows to offer maximum protection. Fleas and ticks are commonly found in varying numbers within the nests and the tunnels.

Through the observations of McCoy and others, the breeding season and the rate of breeding so vitally important as a bionomic factor are fairly well known. Pregnant females may be encountered in December, but the largest percentage (70) may be encountered in March or sometimes in February. By June or July only 1 per cent of the females examined contain embryos. At higher altitudes, the breeding dates are later and the season still more restricted. The number of young per litter as ascertained from counts of embryos, varies from 4 to 11. There is some variation in the size of the litter from month to month. In January it may be as high as 9 and litters of 6 or 7 may be found in June. Furthermore, there is ample evidence that the litters are uniformly larger where a food supply is abundant and the rodent population has been decreased by control operations; all the evidence at hand indicates that each female raises but 1 litter each year. The bulk of the young squirrels make their appearance above the ground with remarkable uniformity in April and May; they reach maturity by September when they are from 4 to 6 months old. The greatest number of squirrels—an average threefold increase or a ration of old adults to young of at least 1 to 4—are usually present in June when the young first appear, then a gradual decline in numbers takes place so that by the end of October usually 80 per cent of the population consists of young of the year. These seasonal densities of the population are normally regulated by the natural enemies of the ground squirrel of which the most important are eagles, red-tailed hawks, coyotes, badgers, weasels, rattlesnakes and gopher snakes. On the other hand, there is considerable evidence, but not a great deal of accurate data, that undue population densities of squirrels in given areas may be controlled by disease. Until recently, the estimates on densities were based on counts taken of living squirrels that happen to be above ground. Season of year, time of day and state of weather will profoundly affect the proportion of squirrels in sight or below ground. Despite these inherent disadvantages it is estimated that about 10 squirrels to the acre represents a maximum infestation, while moderate densities as, for example, 20 to 25 ground squirrels per acre in canyons and draws or, as Long has seen in one instance, an average of 140 to the acre are highly abnormal concentrations. It is their prolific breeding habits and the extraordinary reproductive capacity uncontrolled by the activities of predatory birds and animals that require some other natural agencies for control. There is ample evidence in recent years that the natural enemies, even when little interfered

even for the cycles of epidemics. But in view of the recent observations by Sokhey and Chitre that resistant rodents may be encountered in regions or localities of India proven free from plague, it would be premature to draw such conclusions from the mortality rates of a limited number of experimentally infected squirrels. To subject the 31 different wild rodents of different ages and sexes to comparative susceptibility tests on a significantly large scale represents a gigantic task, but it may have to be undertaken in order to clarify certain aspects of the sylvatic plague problem. The apparent immunity of certain species of rodents, because they escape infection even when living in close contiguity to other infected species, is in part due to their habits, and in all probability to a difference in their flea parasites. Finally, in the laboratory the Oregon squirrels acquire plague readily by cannibalism, but the importance of this mode of transmission under natural conditions has been rarely recognized except at the height of epizootics.

For California, the Beechey squirrel (*Citellus beecheyi beecheyi*) is the principal host for the plague bacillus, and it is believed that the ecology of this rodent should be understood before the more complex relationship in the Boreal and Transition Zones are investigated. Attention has therefore been focused on this rodent.

The term "Digger" squirrel is often applied to this species, more especially in the foothills and mountain regions, in recognition of its burrowing habits, to distinguish it from the tree-inhabiting gray or red squirrels. Essentially ground-dwellers, relatively large in size with long bushy tails and generally grayish coloration with a three-cornered silvery patch on each shoulder, this species is restricted mainly to the state of California. It is most abundant on the plains of the San Joaquin Valley and in the Coast Ranges and Sierra foothills, the life zones lie in the Lower and Upper Sonoran. It populates much of the best farming and grazing lands in the State, and was considered a pest to the farmer at the early date of 1808 when, according to Bancroft, about a thousand of these animals were killed in 9 days at the Santa Barbara Mission. This squirrel secures shelter for itself and young and safety from its enemies by burrowing in the ground. It chooses to excavate its retreats in hillsides or in low earth banks, but in granite country it makes its home under large boulders or in rock taluses where a minimum of burrowing is necessary to ensure safe retreats. The extent, diameter and depth of these retreats vary greatly and depend largely upon the nature of the soil. Tunnel excavating is carried on during the spring months, and is shown by the mounds of fresh, soft earth accumulated at the mouth of the burrows. The animals travel to and fro between their holes and their feeding grounds, frequently traversing the same courses until radiating trails are worn through the grass.

In foraging for seed pods, grain or fruits, they stuff the food into capacious cheek pouches. They repair to some point of vantage to hull and devour the food. Three general types of burrows have been recognized. The males live in shallow, simple burrows at the outskirts of the "colony." A burrow of a female with young is a complicated system of tunnels with many "blind alleys."

normal hosts for several species. Beecheyi squirrels on the observation range at Calaveras Dam (Hooper Foundation plague studies) carried *Diamanus montanus* and *Hoplopsyllus anomalus* in varying proportions. Of approximately 7 500 fleas collected, only about a dozen belonged to other species (Stewart and Evans). This striking host preference may extend to biologically related rodent species or groups. The importance of this preference in the dissemination of the plague bacillus is quite obvious particularly in the light of another fact, namely an interchange of parasites brought about by a fleeting environmental contact of the various rodents inhabiting the same region. As the tedious ecological studies progress, it has been noted that many of the insects attach themselves only while feeding. In consequence, it is difficult to secure a true picture of the ectoparasitic fauna (flea index) by merely counting the fleas found on the wild rodents above the ground. Either excavation of the nests or the collections at the burrow openings from pieces of cotton batting according to a method devised by Stewart and Evans, will give a fairly accurate picture of the flea population density in the nests and the species composition on the host. In general there is a relationship between the number of fleas infesting rodents and the parasite density in their nests. Epidemiologically, of importance is not only the seasonal density but the *seasonal flea species composition*. Since the data to be presented strongly suggest that the vector efficiency of the different species of fleas may be quite variable, the potentialities for sylvatic epizootics might be predicted from the species composition of the flea population by collecting specimens from the burrow openings.

The incidence of flea infestation is quite variable and certainly not determined by host size. For example the Beecheyi squirrels show a marked increase in the magnitude of flea infestation beginning in August and still increasing in October. On the other hand, the indices on chipmunks—*Eutamias*—indicate a rise in July with a peak in the second week in August. The Sierra Nevada chickaree, also one of the high altitude rodents, differs from all other hosts in that its flea index is higher from the second week in June to the last week in July. However, a more or less constant flea population level is maintained on a rodent over a period of time, not great enough to involve factors capable of exerting an influence upon the bionomics of the fleas sufficient to bring about a change in the size of the general population. Since fleas are active in seeking hosts, a rodent freed from all fleas will acquire what appears to be the normal number for that particular season of the year in a very short time, possibly within a few hours. At the Calaveras observation area a distinct seasonal incidence exists between *Diamanus montanus* and *Hoplopsyllus anomalus*. The former was markedly predominant during April and June while the latter overshadowed numerically the *Diamanus* from July and October while the mean temperature was above 75°F. Analogous conditions with minor fluctuations exist in other areas thus far studied.

Concerning the bionomics of the different species of ectoparasites very little is known, in fact, the most important vector—the ground squirrel flea—*Diamanus montanus* is in the process of being investigated. Many of the unknown

with by man, have failed to exercise any appreciable influence on the reproductive rate of the rodents, and that consequently plague had assumed the function of a check on their numbers

A period of dormancy—a form of aestivation to true hibernation—has been observed for the adult ground squirrels when they become exceedingly fat, young adults, less than a year old, remain active throughout the winter in the lowlands. Thus, it is readily explainable why plague may be found in December and January, a fact which prompted McCoy to the statement that there is no seasonal prevalence of *P. pestis* infection among squirrels

The recently completed ecological observations by Evans and Holdenried prove the sedentary nature of the ground squirrel population. By recording the movements of 433 marked squirrels, it was found that the greatest distance moved was about 1,300 yards. Young squirrels showed a greater tendency to move, and the movements are exploratory rather than migratory in nature. Furthermore, as Grinnell and Dixon have noted already in 1918, "there is nothing to show that there has been either extension of the general range of species or any retraction in it either." Applied to the problem of the supposed spread of plague from one focal center to another, it must become quite evident that in the state of California it did not spread by migration, but it is due to a process of contact between individuals in a continuous population composed of many host species (Evans). As a whole, in the regions studied, the dispersal has been a very slow process. Thus far, these facts are only known for one or two species of *Citellus*. Moreover, one does not know the factors which limit the normal dispersal, how a search for mates mixes up the rodent population, or how aestivation and hibernation limit all these activities has not been determined.

Thus far, attention has been focused on the primary host—the squirrel. Little data is available concerning other species of rodents. Complex ecological relationships are created when several species of rodents occupy the same burrow system and the ectoparasite infested nests, either temporarily when in danger or after the death of squirrels. The importance of mice and wood rats is quite evident, but little is known concerning the rôle of predatory and scavenger birds as studied by Jellison, particularly with respect to the spread of infected fleas.

These different observations, to be supplemented by various ecological methods, ultimately will furnish data relative to rate of increase of a squirrel population, and thus provide some means of relating outbreak of epizootic disease with a certain density of population.

(b) *Flea Population Studies* It is well known that the pestiferous fleas vary according to the species of wild rodents, each has its own hordes of *Pulexidae*, *Ceratophyllidae* and *Leptopsyllidae*. Over 50 different species have been found on the Western wild rodents (Eskey and Haas). Needless to emphasize, the number of fleas varies per animal and according to the seasons. Early in spring or late in fall, individual squirrels caught above ground may harbor over 50 fleas, occasionally a sick animal may be covered by 300 parasites. For certain rodents, an average of 20 while for others 10 or even 1 flea may be considered an average fauna. Many rodents harbor only one species of flea whereas others are the

while of 49 *Xenopsylla cheopis* only 14 or 29 per cent, became infective. An infective flea may transmit *P. pestis* on repeated feedings on separate hosts. The mean number of transmissions effected by a group of infective individuals is known as the *transmission potential*. As a segment of the great problem which involves the evaluation of the various fleas as vectors, it has become customary to designate *Xenopsylla cheopis* as a very efficient vector and on the other hand *Malacacus telchinum* (Roth) from *Microtus* as either incapable of transmitting plague or, at least, a very feeble vector. From the preliminary studies on three species of fleas, it is recognized that neither a high *infection potential*, namely the acceptance and implantation of the *P. pestis* in the alimentary canal of the insect, nor the *vector potential* alone without a consideration of the *transmission potential* is indicative of high vector efficiency. To be sure, it appears not unlikely that some of the wild rodent fleas as, for example *Diphanus montanus* may be more efficient vectors between rodents than the rat fleas which have the reputation of great efficiency. The second most frequent ground squirrel ectoparasite—*Hoplopsyllus anomalus*—is a very poor vector in the light of these comparative studies. However, it must be emphasized that the fleas in all these experiments are regularly fed, and therefore held under conditions that do not resemble those met in nature. The studies on the wild rodent fleas have proven again the importance of the *incubation time* which must elapse between the implantation of the plague bacillus into the intestinal tube of the flea, and the ability of the insect's bite to become infectious. In the different experiments reported, this interval varied considerably, Eskey observed an interval of from 3 to 130 days, while Douglas and Wheeler noted an elapse of from 4 to 19 days or an average of 9.6 days, that it is influenced by the temperature of the environment and perhaps other factors needs no emphasis. In the ecology of plague, the rapidity with which a flea must become infective is probably a determinative force with which the spread is maintained or enhanced. The life span of the plague "infected" and 'infective' flea is likewise determined by many environmental factors. As a rule, "infective" fleas are unable to feed properly and they may succumb on the average within 5.4 days (0 to 50 days) after the first transmission while the infected insects may play host to the plague bacillus without noticeable ill effects for the normal length of life characteristic for the species (Douglas and Wheeler). What this time is has not been determined with any degree of accuracy under natural conditions, particularly when starved. Although the single flea transmission efficiency tests conducted in the laboratory have given inconclusive or negative results with the second most common flea of the ground squirrel—*Hoplopsyllus anomalus*—the routine tests with ectoparasites collected in nature of inoculating guinea pigs with the triturated fleas, have proven this species to be infected. In addition to *Diphanus montanus*, *Echidnophaga gallinacea* removed from burrowing owls (*Speotyto cunicularia*) in Kern County have also yielded plague infections in tests on guinea pigs (Evans, Wheeler and Douglas). The vector efficiency of this flea has not as yet been established, it may prove of interest in view of the observations of Jellison that the nests of these birds house an abundance and variety of rodent fleas. As "preservers"

factors in sylvatic plague are intimately related to the influence of the climatic conditions on the life and longevity of the insects. The "microclimate," the temperature and humidity of the burrow exert their influences on the life-cycle of the flea, and thus on the death-rate of the insect and indirectly on the behavior of the plague bacillus within the body of the ectoparasite. In order to comprehend the importance of these factors, the mechanism of *P. pestis* transmission through the agency of the flea must be understood. The early transmission experiments by Ogata and Verbitski and the studies of the Indian Commission have all been conducted by placing a number of the parasites in a cage with a sick animal and, subsequently, allowing them to feed on healthy hosts. When it became necessary to understand the mechanism of transmission, Bacot and Martin (1914) experimented with individual fleas. It is this procedure which, in recent years, has been employed by Eskey and Haas, Wheeler and Douglas, and the Russian workers, Golov and Ioff and Bychov, in determining both the ability of the wild rodent fleas to accept the plague bacillus and to convey it to the mammalian hosts. To date, approximately 32 species of fleas collected from American wild rodents have been tested and found capable of accepting an infection provided they were given a meal on a guinea pig or mouse, marmot or gerbille which presented a terminal plague septicaemia of a few million bacilli per 1 cmm of blood. The infection of these fleas is proven by the presence of plague bacilli, which are recovered from the faecal droplets discharged by the parasites. To demonstrate this elimination of the bacteria, the culturing of the vial content in which the fleas are kept with gentian violet broth (Meyer and Batchelder) has proven most valuable. The infectiousness of these cultures is confirmed on white mice or guinea pigs. Bychov and Borzenkov investigated the existence of an infection of fleas by extracting the intestinal tract and by seeding their contents on agar plates. Individual fleas and certain species rid themselves of the bacilli within a variable elapse of time as had been demonstrated by the Indian Commission. The nature of this cleaning process of "infected" fleas is not understood, it may well be conditioned by the genetics of the host. This "purification" process may be so thorough that the inoculation of the crushed flea into a susceptible guinea pig fails to produce disease. Fleas, having cleansed their intestinal canal of plague organisms, as a rule, may repeatedly dispose of bacilli which they ingested in subsequent infectious blood meals. However, just as George and Webster had already demonstrated for the rat flea *Xenopsylla cheopis*, that only under the most favorable conditions, a few of the "infected" fleas become "infective," capable of infecting through the bite, so have the studies on wild rodent fleas by all recent workers established a similar behavior. In the tests made by Eskey and Haas, only 13 species of fleas from wild rodents in North America transmitted by their bites. This ability to become infective has been designated by Wheeler and Douglas as the *vector potential*, and represents the percentage of infected individual fleas to become "infective." For two species of laboratory reared fleas—the rat flea—*Xenopsylla cheopis* and the squirrel flea—*Dipentulus montanus*—this potential has been established. Of 41 *Dipentulus* 21 or 52 per cent,

viable in the ticks for at least 11 days and the faecal droppings were infectious even for longer periods. Inquiries into the role of ticks as preservers of the plague-contagion in the burrows are urgently needed.

Through the efforts of M. A. Stewart and in the course of flea surveys in the vicinity of cities, dependable data relative to the exchange of fleas from their natural to aberrant hosts have been collected. There need be no doubt that squirrel fleas are picked up by rats and dogs, and the reverse—a transfer of rat fleas to squirrels has been definitely proven. Some of the documentary evidence along these lines is as follows. *D. arcanus montanus*—in all probability the vector par excellence—has been collected from *Neotoma*, *Rattus norvegicus* and *Neotoma* in the San Francisco Bay Los Angeles (1924) and Salt Lake City areas *Rattus rattus alexandrinus* and *Neotoma cinerea occidentalis* and marmots in Oregon, rock squirrels, tree squirrels and prairie dogs in Colorado and the wolverine in British Columbia. In the surrounding territories of Los Angeles the *D. arcanus* index on rats in 1933 varied from 1.64 in Whittier to 4.4 in Pomona (R. V. Stone). *Hoplopsyllus anomalus* was likewise demonstrated on *Neotoma* rats in San Francisco and the cotton-tail in Monterey County. Beecheyi squirrels caught in the Belvedere district of Los Angeles carried on the average 3 *Xenopsylla eretopis* (R. V. Stone), similar findings have been reported from Salt Lake City.

V. RODENT PLAGUE EPIZOOTICS

Preliminary field studies on the course of squirrel epizootics in Kern County were made in 1934 and the essential facts have already been sketched in the historical review. Annual surveys from that year on were negative until 1941, when plague was again demonstrated both in squirrels (*Sciurus harrisi*) and in several species of fleas (*D. arcanus montanus*, *Hoplopsyllus anomalus* and *Ectoprotaga galinacea*). Sylvatic plague was found in five separate and distinct localities. According to the field studies of Evans, Douglas and Wheeler, each focus acted as a unit by itself, for each is at least 15 or 20 miles distant from any other located within the foothill area. Careful surveys of the intermediate stations failed to reveal the presence of *P. pestis*. No evidence of spread from one focus to another was observed. Focal occurrence and discontinuous distribution is apparently one of the characteristics of sylvatic plague.

The first specimens positive for plague were obtained by the California State Department of Public Health Crews on April 24 while the last positives were taken on July 17 subsequent surveys yielded neither infected rodents nor fleas. Important is the fact that *P. pestis* was demonstrated in fleas before it was found in squirrels and considerably after the last positive squirrel. Thus the active disease in the squirrel was extremely short in fact, the entire epizootic which eliminated on one ranch close to 90 per cent of the squirrel population, lasted approximately 3 months. Of the 2,494 squirrels shot within and surrounding the plague epizootic area 16 or 0.64 per cent proved positive for plague. Thirty-nine pools of fleas from a collection of 17,958 ectoparasites were positive. But excavations of 54 burrows and the examination of 38 revealed the carcasses of 44 squirrels just at the entrance or on the mounds outside. Hence it is quite

of the plague bacillus, these fleas may have some function. In the course of a rodent epizootic, the prairie or veldt is probably saturated with "infected" fleas. According to Ioff and Pokrowskaja, 63 per cent of the insects collected were found to be infected, in fact, a normal healthy squirrel carried a dozen infected fleas. Unfortunately, no data concerning the North American fleas in an epizootic area are available, although Eskey and Haas (page 51) selected through microscopic examination 20 fleas from prairie dogs and found 14 plague-infected.

The process by which the infective wild rodent flea conveys the infection to the vertebrate host differs in no way from that already established by Bacot and Martin for the rat flea and for the sushik flea—*Ceratophyllus tesquorum*—by Golov and Ioff. Regurgitation of blood from the oesophagus, due to bacillary mass formation and obstruction in the proventriculus, has been regularly observed in mounted fleas (Eskey and Haas). Microscopic sections reveal clearly the progressive accumulation of bacterial clumps and the development of the blockage (Douglas and Wheeler). Not only in the stomach but in the intestines and the rectal pouch an identical multiplication may be noted. Of interest is the fact that fleas with an apparent block will occasionally establish a normal flow of the ingested blood and thus resume normal feeding habits (Douglas and Wheeler).

As other modes of transfer of the infective agent, the Russian workers, Tuman-ski and Poliak and Bychov, consider, in analogy to the findings of the Indian Plague Commission the following modes for the wild rodents: (a) Crushing of the infected fleas with the teeth and infection through the buccal cavity; (b) Scratching and rubbing of infected fleas, rarely faecal droppings into superficial skin wounds or abrasions; (c) Through the bite of the flea with a soiled proboscis following the sucking of blood from a diseased rodent. Recent experimental attempts to imitate these modes of transmission have thus far been unsuccessful (Eskey and Haas, Wheeler and Douglas), however, in the early studies by the Russian workers, Golov and Ioff, the ingestion of fleas is repeatedly emphasized. Under natural conditions due to the great mobility of the fleas, these transfers of the plague bacillus are probably quite rare.

The louse—*Haematopinus columbianus*—and a variety of ticks, inhabitants of the squirrel burrows, have been found capable of harboring plague bacilli (McCoy and Borzenkov and Donskov, Eskey and Haas, Douglas and Wheeler). Their position in the ecology of sylvatic plague is not clear. There is no conclusive evidence that they act as vectors, their infection merely attests that they had fed on plague-infected animals. In one experiment Jettmar succeeded in infecting a healthy squirrel by placing upon it tarabagan lice—*Lanognatoides citelli*—collected from a dead artificially infected tarabagan. One recalls in this connection the important fact that bedbugs—*Cimex lectularius*—may carry plague bacilli in the intestinal canal for at least 147 days (E. I. Novikova and G. A. Lalazarov). According to Borzenkov and Donskov who found infected the tick—*Rhipicephalus schulzei*—on *Citellus pygmaeus* or in its nest, and who experimented with *Hyalomma volgensae* report that direct bites of these insects may cause infection and death in healthy animals. Plague bacilli remained

endemicity or more specifically on the persistence of plague. Although the Russian workers give no answer to the pertinent question 'How does this endemicity arise?' they do point out that wherever there is a given species of rodent in sufficiently large numbers, 'a chance introduction of infection by other animals or by man can lead to the formation of a new center'. What these animals may be is not stated but the rat (*Rattus norvegicus*) is mentioned. Nevertheless the history of a plague center usually dates back so far that, with few exceptions, the origin cannot be determined. There is ample evidence that when constant impediments are missing the enzootic center slowly but definitely spreads. Since it is invariably the epizootic in the enzootic regions which is responsible for the spread and the creation of new centers it is of practical importance that the rodent control must concentrate its efforts on the active area, provided it is recognized early in the course of evolution. It is regrettable that this principle has not been practical of execution. Only too often, epizootics were recognized in areas which were doubtless enzootics operated for many years, dispensing their harmful seeds long before man ever became interested in the nature of the wild rodent mortalities.

This description, in part at least, explains the spread but gives no account of the quiescent stage, the various factors which prepare the ground for the sudden epidemic rise of plague and the last stage or aftermath. Both these phases must in some way be connected by a mechanism described as the *persistence or perpetuation of rodent plague infection*, or the "carry over" from one season to another. The rôle played by "latent" plague in the hibernating rodent or the infected flea as "preservers" of the bacilli has received consideration under experimental conditions, but the correctness or incorrectness of the observations still has to be proven. For practical purposes, Pirie, who has made dependable field observations in South Africa, believes that the flea is the all-important factor in the *persistence* of plague. When rodents are few in number, the disease would be of a quiet, smoldering type, a squirrel infected every here and there at 2 months interval would be sufficient to keep the disease alive. As the number of rodents increases and the fleas presumably increase in response to environmental factors, contacts would be more easily made and the number of cases would increase. For hibernating rodents, the maintenance and perpetuation of the plague infections during the winter is doubtless more complex. What the ultimate explanation of the "carry over" may be, there is no doubt that the vector-host relationship must be maintained. In the region with hibernating rodents, the underground disappearance of the squirrels may terminate the plague activities for the season, but with the first appearance of the animals above the burrows, the entire process repeats itself this year and the year after with diminishing returns of invisibly diseased animals or pools of infected fleas. At the end of a 3 or 4 year cycle the area has assumed the aspect of non-infected territory only to erupt again within 10 to 12 years with the same intensity as seen on the first occasion when it was studied.

This sketchy survey of the ecology of sylvatic plague has left a great deal unanswered, because knowledge is either not available or it is burdened by hypoth-

evident that the survey operations and the demonstration of plague in the shot squirrels gives indeed an inadequate picture of the intensity of the epizootic. A careful inspection of one focus showed that the majority of burrows had been abandoned because of disease. Although fleas were found at the entrance of 43 burrows, they were discovered in only 15 of the 38 nests which were examined. In August no fleas were present in 4 nests investigated. Ecologically important is the shift in the proportion of *Dipodomys montanus* to *Hoplopyllus anomalus*. The dominant species in the early stages of the epizootic was *Dipodomys*, and later it was in part displaced by *Hoplopyllus*. The absence of this species in the nests is not understood, likewise, the presence of infected fleas in only 1 nest.

Experiments on the rate of decomposition of squirrel carcasses led to the conclusion that the active phase of the epizootic stretched over the months of May and June, or at the height of the dispersion of the young. In order to be guided for the investigation of future epizootics, the published reports by Kalabukhov and Raevskii on the life-cycle of *Citellus pygmaeus*, and the laws governing the development of sylvatic plague epizootics in Southeast Russian endemic region deserve particular interest. The observations are significant and, in general, applicable to the conditions which prevail in the endemic foci of California and, probably, in other plague areas. The ecology of sylvatic plague evolves briefly as follows. Following the appearance of the young squirrels above ground, the density of the population increases 3.2 to 3.6 times, and thus increases the chance of contact. Moreover, with the dispersal from the maternal burrow, the young in searching for habitations become exposed in inhabited or deserted burrows to the flea population which maintains, in all probability, the plague virus from season to season. This dispersion takes about a month, and is influenced by the climatic conditions of the spring. It may begin early or late and thus determines the date of the animal epizootic outbreak which, on account of the physiologically conditioned high susceptibility, renders this stage of the life-cycle—youth—particularly liable to infection. Migration, to be correct, the emigration studies by means of the trapping or the banding method have shown that during the summer season the ground squirrels usually move only short distances, not exceeding a few hundred yards. Spread of the epizootic to great distances in a short time is therefore scarcely probable. However, through the crisscross wanderings over short distances, a gradual contamination of the territory adjacent to the enzootic area follows, and in the majority of cases a spread for from 1 to 3 miles may take place. Just as the high density favors the spread, so does, on the other hands, a low rodent density impede and strangle the extensions of the epizootic, in fact, in many instances it may limit or even liquidate the enzootic area. Since the phases of the life-cycle vary according to the regions in which the squirrels reside, awakening from hibernation, reproduction, dispersal of the young, the state of the vegetation, whether green or desiccated, may be subject to considerable shifts, and therefore may affect the duration and the course of the epizootic. Of importance is the fact that the animal epizootics depend on the

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eses not in harmony with newer ecological thought. Whatever disagreement may exist among experts regarding the efficacy of the suppressive measures against wild rodent plague by shooting, poisoned barley mixed with strychnine or thallium, carbon bisulfide and methyl bromide, it is well to remember that they have had the continuous interest of the California Health and Agricultural authorities for the past 30 years, and still they remain unsolved. However, contrary to the belief too often held by the laity and even by those who are familiar with sylvatic plague, an epizootic among wild rodents is by no means always followed by human *P. pestis* infections. The huge plague regions in Russia furnish many convincing examples. During June, 1913, a severe epizootic affected the squirrel population of the Astrakhan steppes in the vicinity of two villages with a population of 6,000. At least 75 per cent of 1,243 cadavers of susliks and hares scattered over the pastures proved to be plague-infected, yet no case of human plague was diagnosed. Similar situations have been observed in 1930 in the steppes of the Urals. Although the factors influencing this low transmissibility are entirely unknown, these mass observations in conjunction with the experiences in the North American Continent during the past 30 years should help to alleviate to a certain extent the fear which the presence of sylvatic plague continues to create among misinformed groups of people.

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THE ECOLOGY OF PSITTACOSIS AND ORNITHOSIS*

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From a rare and obscure disease human psittacosis, so named by Morange in 1895 though doubtless first observed by Jürgensen in 1876 and definitely described by Rutter (1879) as a typhoid pneumonia contracted from exotic birds, was suddenly raised into a malady of world-wide interest, when in July, 1929, Barros informed a number of prominent physicians and later the Medical Society of Córdoba, Argentina, concerning the appearance of over 100 cases of a serious and peculiar pneumonia among the inhabitants in the province. He diagnosed the infection as psittacosis, since the epidemiologic investigations showed that a large consignment of 5 000 psittacine birds imported into Argentina from Brazil and offered for auction under the most insanitary conditions served as the focal center for the dissemination of the illness. A destructive infection in the light of present day knowledge unquestionably psittacosis had broken out and the managers, anxious to sell as many living birds as possible, disposed of their stocks with great rapidity. Purchasers and re-purchasers auctioneers etc became ill and some died. The auction was then transferred to Tucumán the bird mortality continued, and with it human cases flared up in every quarter of the city. Local attention was directed to the strange disease when several epidemics developed in the capital of Argentina Buenos Aires, during the month of October, particularly when two members of a theatrical troupe of 12 persons died, all of whom fell ill following the use on the stage of a parrot which came from the original importation to Cordoba. These events fully warned the population, and the trade in parrots was stopped entirely in Argentina. However the passengers of steamers calling at the ports ignorant of the existence of an epidemic disease of parrots transmissible to man bought many of the infected birds from unscrupulous dealers. Thus the malady was conveyed to at least 12 different countries. It reached the United States in November, while England already reported cases in July and then in December. During the early months of 1930, the newspapers gave accounts in Austria, Italy, Switzerland, France Denmark Algeria, Holland, Egypt, Czechoslovakia Germany and Sweden. In many of the reports it was stated that shipments of sick parrots had arrived in the countries before the cases were observed. However, a critical perusal of the records of 1930 leaves no doubt that the South American parrots were not the only sources of infection. General interest in the new disease called attention to these infections and what under ordinary circumstances would have been dismissed as an atypical pneumonia was correctly

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quite broad, and hence spontaneous parasitism of many birds and even mammals may be anticipated

In order to assure for the future a more descriptive and uniform nomenclature, it appears desirable to replace the designation psittacosis and select a name which takes into consideration the primary sources of infection, which are not of psittacine origin. The avian infection, which is frequently latent and in its clinical manifestations by no means characteristic, should be described as "*Ornithosis*" (ornis = (ornith) = bird). For the human disease, the same designation would be appropriate. Perhaps, in order to emphasize the specific anatomically distinct type of pneumonia which so often governs the clinical picture, one could use the succinct term "ornithotic pneumonia" or "pneumonia ornithosa." Haagen and Mauer, guided by similar ideas, suggested the replacement of the designation psittacosis by "virus pneumonia" or epidemic pneumonia. The latter would distinguish the psittacosis pneumonia from that caused by bacterial agents, but such a proposal does not take into consideration the fact that, aside from the specific influenza pneumonia, other virus pneumonias have and will be discovered. An endless confusion would follow. In future, it may be advisable to record with an appropriate adjective the origin of the virus as, for example, "psittacine" ornithosis and "columbidian" ornithosis. In this lecture the designation psittacosis is used to indicate an infection with a definitely proven virus of psittacine origin, while ornithosis describes human and bird infections due to psittacosis-like agents of non-psittacine derivation.

The knowledge concerning psittacosis and ornithosis which has accrued during the past 10 years, although still incomplete in a number of details, unrolls an intriguing interaction of a virus, parasitism in birds, and environmental factors, which ultimately led to accidental infections of human beings. There is no doubt that ornithosis, like plague, is a self-regulatory ecological multiple factor phenomenon, which is capable of description. Such a deductive epidemiologic narrative is attempted in the paragraphs which follow.

I THE "VIRUS" AND THE METHODOLOGY OF ITS DEMONSTRATION

The hypothesis of Nocard (1892) that the avian disease responsible for the human infections in the Paris epidemic studied by Dubief (1893) is in some way connected with the gram-negative motile bacillus (*S. typhi murium*, Bambridge, 1912) he had cultivated from the bone marrow of the dried wings of parrots that had died on the voyage from South America, failed of confirmation, since neither Nicolle in 1898 nor any of the subsequent investigators were able to find it in the excretions or tissues of fatal human infections. Independently in 1929-1930 and in rapid succession by Krumwiede and his associates, Armstrong and McCoy in the United States, by Levinthal in Germany, Bedson and Western in England, and Sacquépée in France, the filterable "virus" character of the disease agent in the splenic and hepatic emulsions from parrots and humans suffering from this malady was established. With sterile filtrates, the disease was reproduced in healthy birds. Of particular importance and as an invaluable aid to psittacosis and ornithosis research was the discovery by

diagnosed as psittacosis. In England, the United States, Austria and Switzerland parrot fever was observed to develop following contact with lovebirds and canaries. The pandemic era of 1929-1930 with approximately 750-800 human cases of psittacosis was abruptly terminated when in the early months of 1930 the public health agencies of every country that had been affected established either stringent import regulations, or quarantine restrictions prohibiting the admission of any birds belonging to the large group known as the "Psittaciformes."

With the discovery by Meyer and Eddie in 1931 and 1932 of a wide distribution of latent psittacosis in the local breeding establishments and aviaries of California, subsequently likewise recognized in Germany by Fortner and Pfaffenberg, in Austria by Gerlach, in France by Aujaleu and Jude (1936), in Holland by Ruys (1933), in England by Levinthal and in Canada by MacNabb (1941), the endemicity of the infection involving another 600 human victims and the examination of thousands of psittacine birds offered a splendid opportunity to many investigators for a thorough study of the disease from a clinical, etiological and epidemiological point of view. Once the clinical picture of psittacosis had become familiar and laboratory methods for its diagnosis had been developed, further cases not associated with South American parrots or parakeets continued to be recognized. Canaries and finches were occasionally responsible for human cases of psittacosis. When Meyer and Eddie found that several birds in a cargo of native Australian budgerigars were infected when they arrived in California (1934), although there had been no contact with any known source of infection, and when further two consignments of Australian parrots heavily infected with psittacosis had arrived in London (Levinthal, 1935), Burnet initiated his detailed investigations on psittacosis in wild Australian parrots. Evidence of the disease was proven in each important group of the true parrots, the lorikeets and the cockatoos. Thus, the parrot-man infection chain appeared to constitute the sole problem and the order of Psittaciformes the principal reservoir of infection, while certain highly susceptible species of finches and canaries became diseased merely through contact with diseased parrots or parakeets. This belief was soon recognized to be ill-founded when Haagen and Mauer in 1939 had shown that in the Faroe Islands the fulmar or petrel (*Fulmarus glacialis*) is infected, and is the source of human cases. The epidemiologic investigations in progress since a fatal case of human psittacosis in California was traced to racing pigeons and another case in New Jersey to a flock of chickens owned by the patient, have in recent months disclosed in the ubiquitous pigeon lofts an even larger reservoir of the virus than that demonstrated in all the parakeet aviaries combined. In the differential diagnosis of atypical pneumonias, since psittacosis is influenza-like in its course and is not influenced by modern chemotherapy with sulfonamide drugs (Rudd and Burnet and Meyer), the infection becomes increasingly more important. Where febrile disease occurs in man apparently as the result of contact with any type of birds, psittacosis will have to be borne in mind. The known infection spectrum of the infective agent is

safe reagents may be prepared by simply boiling suspensions of the elementary bodies. Furthermore it is of practical interest that one antigen fraction may be common to the virus particle of lymphogranuloma venereum, trachoma. Not resistant to glycerine it withstands desiccation for months and remains active at very low temperatures (-76°C) for over a year. It is quite labile to heat (15 minutes at 70°C). The infectiousness of sputa or organs is markedly reduced by the deleterious effect of microbial activities.

Experimentally the virus is transmitted to a variety of psittacine birds, finches, canaries, pigeons and chickens, it should always be borne in mind that these birds may carry latent ornithosis or *Salmonella* infections which may lead to erroneous findings. Moreover, in the infected state they are dangerous sources for the only too frequent laboratory infections. The white mouse, preferably a strain highly susceptible to bacteria and not necessarily to neurotropic virus infections, has displaced the birds as a universal and relatively safe experimental animal except in rare instances when the Java ricebird (*Munia oryzuora*) offers advantages. As a rule, the specimens consisting of sputum samples, organs (lung, spleen and liver) of man and of birds (spleen, liver and kidney) in the form of extracts or carefully pulped emulsions in broth are injected intraperitoneally. The experimental disease in the mouse induced by a "psittacine" but not by a 'columbidian' virus is very characteristic. According to the amount injected and the infectiousness of the virus the animal succumbs after 2 to 30 days. An enlarged spleen, liver necroses, a serofibrinous peritoneal exudate with abundant virus elements in the reticulo-endothelial cells, occasional patches of pneumonia resulting from a destruction of endothelial cells, and sterility of the organ suspensions on the usual culture media prove the psittacosis nature of the infectious process. When the virus is of *low infectivity* for mice enlarged spleens without any definite elementary bodies may be suggestive of the ornithotic virus. It is then advisable to test for the infective agent by *intracerebral* and *nasal* passage administration of splenic emulsions. The enrichment of the M M P bodies in the meningo-choroid structures or in the lungs furnishes smears which are diagnostically definite and conclusive. Mice inoculated subcutaneously with small doses of virus or fed with it may survive the infection for over 400 days and exhibit a sterile or non-sterile immunity. Extensive and highly characteristic pneumonic lesions may be induced by intratracheal injection of guinea pigs (Fortner and Meyer and Eddie), rabbits, squirrels (Meyer and Eddie) and monkeys (Rivers and Schwentker). These animals are of little value in the primary isolation of the virus or in diagnostic work, however, they are frequently used for immunity studies. Virus passages through mice stabilize the infectivity and maintain it for hundreds of generations. The epidemiology of human psittacosis or ornithosis depends upon the demonstration of the specific agent in the sputum (Rivers and Berry) or blood (Bedson, Meyer and Eddie), or the spleen or lung of the patients. At any stage of the disease the sputum is the most likely material to yield positive findings on inoculation of unfiltered centrifuged sputum extracts in broth into mice and in order to overcome the pneumonic flora which may be present, into ricebirds.

Krumwiede, McGrath and Oldenbusch that the virus is readily transmitted to white mice. Furthermore, in view of the fact that only filtrates through the coarser grades of Chamberland candles were infectious, the virus particles were promptly demonstrated by a number of workers in the early months of 1930. These bodies generally described as *Levinthal-Cole-Lalhe* bodies (L C L bodies) measure 0.22 to 0.3 μ , are readily demonstrable in the exudates, blood and organs of diseased birds, mammals and man. Their microchemical reactions (readily stained by the Macchiavello or Castaneda technique for rickettsias, with Giemsa, haematoxylin), and their morphology as well as the multiplication within reticulo-endothelial cells or cellular elements of tissue cultures places the bodies more in the group of bacteria than the true viruses. By comparison with other morphologically visible viruses their position is unique (Robinson and Bland). They are both Feulgen and Castaneda positive, while the virus of lymphogranuloma is only Castaneda positive. The vaccinia particle is not demonstrable by either method.

The microscopically discernible development stages of the particles show within the invaded cells an early matrix ("plaque" of Bland and Canti, "inclusion body" of Levinthal) in which the elementary bodies develop in great number, these virus colonies release the minute coccid bodies or the *Microbacterium multiforme psittacosis* (M M P bodies). From a historical point of view the claims of Levinthal, who saw the great variability in the size of particles, must be recognized, and the name proposed by him deserves preference over the designation L C L bodies (Yanamura and Meyer).

The number of elementary bodies encountered in infected birds, mammals or man may vary greatly. Usually in acute experimental infections in birds and mice they are readily seen in the spleen, liver, lung or brain lesions. In human material, in birds and in mammals, or when multiplication is restricted as, for example, in older infections of resistant individuals, the few bodies which may be seen are difficult to identify. These elementary bodies may be obtained in a high state of purity by fractional sedimentation of organ emulsions or from cultures in an angle centrifuge. They grow freely on the chorion-allantoic membrane of the chick where they produce pock-like lesions (Burnet and Rowntree), or in liquid and on solid media of the Zinsser-Fitzpatrick-Wei type. Although growth may be typical and abundant, the infectiousness for mice and birds may gradually decline after 300 passages. No evidence for multiplication in lifeless media devoid of viable cells has been presented. As isolated elements, they are readily agglutinated by specific antisera or serve as suitable antigens in the complement fixation test. Since the infectivity depends on the number of elementary bodies present in the infective filtrate and since filtrations through collodion membranes which retain the particles are non-infectious, it is now generally believed that the *Microbacterium multiforme psittacosis* is the actual virus and the cause of ornithosis. Concerning its antigenic composition, relatively little is known, though the studies by Bedson disclosed a component which is resistant to boiling, while another is rapidly destroyed at this temperature. Since the heat resistant antigen is involved in the complement fixation test,

TABLE 1

Relationship of Infection and Complement Fixation Antibodies in Spontaneous Avian Psittacosis

SPECIES		VIRUS ISOLATED		COMPLEMENT FIXATION TITER	
		Organisms	Isolates		
Red or pennant lories, <i>Platycircus elegans</i>	1	— — — — — SLL	0	1 64	— — — — —
	2	— — — — —	— — — — —	1 32	— — — — —
	3	— — — — —	— — — — —	1 64	— — — — —
	4	0	0	1 32	— — — — —
	5	0	0		0
Alexandrine ringneck <i>Psittacula eupatria</i>	1	— — — — —	0	1 64	— — — — —
	2	0	0	1 8	— — — — —
Red rump, <i>Psephotus</i> <i>ruficollis</i>	1	0	0		0
	2	— — — — —	— — — — —	1 128	— — — — —
	3	0	0	1 256	— — — — —
Spectacled parrot, <i>Arazona</i> <i>coloratus</i>	1	0	0		0
	2	— — — — —	— — — — —	1 2	— — — — —
	3	0	0	1 8	— — — — —
Macaw <i>Ara macao</i>	1	0	0	1 128	— — — — —
	2	0	0	1 256	— — — — —
	3	Not tested	Not tested	1 128	— — — — —
	4	Not tested	Not tested	1 64	— — — — —
	5	Not tested	Not tested	1 64	— — — — —
	6	Not tested	Not tested	1 32	— — — — —
	7	Not tested	Not tested	1 32	— — — — —
	8	Not tested	Not tested	1 64	— — — — —
	9-14	Not tested	Not tested		0
Cockateel, <i>Nymphicus</i> <i>volucerrimus</i>	1	— — — — —	0	1 4	— — — — —
	2	— — — — —	— — — — —	1 16	— — — — —
	3	— — — — —	0		0
	4	0	0		0
	5	— — — — —	— — — — —	1 8	— — — — —
				1 16	— — — — —
	6	0	0		0
	7	0	0		0
	8	— — — — —	— — — — —		0
	9	0	0		0
	10	0	0		0
	11	— — — — —	— — — — —	1 4	— — — — —
	12	0	0		0
	13	— — — — —	0		0
	14	— — — — —	— — — — —	1 2	— — — — —
	15	— — — — —	— — — — —	1 102	— — — — —
	16	0	0		0

Unfortunately, the virus is not always present and repeated examinations are essential. Even under ideal conditions of collecting and shipping of specimens, less than 50 per cent of the sputa, when they are obtainable, are infectious.

The complement fixation test with heated antigens prepared from spleens of infected mice (Bedson) or cultures (Meyer, Eddie and Yanamura) has proven of inestimable value in the early diagnosis of the disease provided the patient does not suffer from an inapparent infection with the virus of lymphogranuloma venereum usually indicated by a positive Wassermann reaction (Rake and associates). Already on the 8th day, a reaction of 1:4 and a rapidly rising titer up to 1:256 within the next 15 days has invariably been associated with true psittacosis or the ornithotic pneumonitis infections (Meyer and associates). A persistence of the antibodies has in many patients permitted a confirmation of the clinical diagnosis in retrospect.

The mouse inoculation method is equally useful in the search for the virus in birds, it is advisable to inoculate emulsions of the organs separately or to include in the pools portions of spleen, liver and kidney. Since the virus is frequently found in the cloacal content, suspensions of this portion of the intestines may be tested provided cultures on brilliant green media have proven the absence of *Salmonella typhi murium*, an organism frequently present in South American parrot species and locally raised pigeons as an independent inapparent infection, or as an infective agent accompanying a latent or acute avian ornithosis. Filtration through collodion membranes (450 m μ) must then be made, and the bacterial sterility of the filtrate determined before the inoculations are made. Early studies designed to apply the complement fixation tests to the diagnosis of bird infections proved unsatisfactory, particularly when the weakly antigenic splenic suspensions of mice were employed as antigens. With the use of cultures first as cocto-antigens from Rivers-Li cultures and more recently from crude suspensions of cultures on Zinsser-Fitzpatrick-Wei media (Yanamura and Meyer) the results were different and diagnostically invaluable as indicated by the data summarized in Table 1.

Infected psittacine birds, finches and pigeons give definite complement fixation reactions. They may be strongly (1:128++++) to moderately positive (1:2 to 1:4++++) in birds which harbor the virus in a latent state in the spleen, liver, kidney and cloaca. In larger parrots and pigeons the serum reactions are usually positive in higher dilutions than in parakeets. Sera of immature parakeets with virus demonstrable in the tissues may contain no antibodies. Similar observations have been made on sera obtained from cockateels (about 15 per cent) and pigeons (probably 50 per cent, actual number unknown due to difficulties in isolating the virus). For the present, there is no satisfactory explanation for the inconsistencies. One would have to consider three possibilities: (a) In immature parakeets, which are infected but without serum antibodies, immunological immaturity may play a rôle, (b) the infections are in their early stages, or (c) circulating antibodies are temporarily of a low level at the time of bleeding. Irrespective of these apparent discrepancies, the complement fixation test is most useful in the detection of psittacosis or ornitho-

to consist of infected birds. That the serum antibodies may persist, although the organs are apparently free from virus is not surprising when it is realized that their production may be reactivated by the constant exposure of the birds to small doses of virus in an infected aviary, or that the virus may be present in subinfective doses in the tissues examined. In practice the complement fixation test on avian species is most useful to detect quickly the existence of psittacosis or ornithosis in a group of birds and to segregate the infected from the non-infected. The latter must by necessity be subjected to repeated tests after they have been separated from the infected lot. Experience has taught that at the end of 2 months, if no antibodies develop in their sera they are non-infected and may be safely released. Birds which give positive reactions should be destroyed even though they may, by the end of 1 to 2 years in isolation, free themselves of the virus and the serum may then become negative. The use of the complement fixation test in the epizootiology of avian psittacosis has two disadvantages (a) the handling and bleeding of parrots endangers those who are not immune; it should only be entrusted to persons who give serological evidence of a past inapparent infection or to those who wear properly constructed masks; and (b) it is impractical to secure enough blood from the wing veins of birds the size of parakeets but since the legal control measures require the laboratory examination of the sacrificed birds, the blood tests supplement the anatomical inspections and the inoculation tests on mice. To protect valuable bird collections in zoological gardens the routine quarantine procedures to which imported birds are customarily subjected may be shortened and may be made more effective through application of the serum tests. As a tool to establish the existence of ornithosis infection in pigeon lofts it is invaluable. The technique for testing chicken sera has not as yet been perfected; in its place the agglutination test gives useful information.

II THE PARASITISM OF THE VIRUS IN PSITTACINE BIRDS

One of the important contributions of recent years is the recognition that close to 50 species belonging to five large orders in the class Aves may spontaneously be infected with the psittacosis virus. This distribution of a vast reservoir of the virus is presented in Table 2 but it is important to emphasize that it cannot be considered by any means complete. With the application of newer methods of investigation the existence of psittacosis in species not as yet recognized or listed must be expected and kept continuously in mind. In fact the phylogenetic study of the natural hosts of psittacosis or ornithosis is still a problem to be solved. The course of the infections has been observed and studied on a relatively few. Since the shell parakeet (*Melopsittacus undulatus*) has played a prominent role, data concerning the natural history of this representative of the family Psittacidae may be of general interest.

Shortly after the recognition of the existence of psittacosis in the aviaries of California a large number of the shell parakeets were brought to the laboratory for observation and examination. These birds had been known by many names in the past such as zebra parakeets, undulated parakeets, warbling

TABLE 1—*Concluded*

SPECIES		VIRUS ISOLATED		COMPLEMENT FIXATION TITER
		Organs	Intestines	
<i>Cockateel, Nymphicus hollandicus</i> —Continued	17	0	0	0
	18	0	++++'	1 3 +++++
	19	++++	++++	1 128 +++++
	20	Not tested	Not tested	1 20 +++++
	21	Not tested	Not tested	1 48 +++++
	22	Not tested	Not tested	1 2 ±
	23	Not tested	Not tested	1 10 +++++
	24	Not tested	Not tested	0 Paratyphoid
	25	Not tested	Not tested	0
Mask, <i>Agapornis personata</i>	1	0	++++'	1 2 +++++
	2-26	0	0	0
Cockatoos, <i>Kakatoe galerita</i>	1	++++	0	1 128 +++++
	2	0	0	1 64
	3	++++	0	>1 128
Cockatoos, <i>Kakatoe sanguinea</i>	4	0	0	0
	5	0	0	0
Cockatoo, <i>Kakatoe roseicapilla</i>	6	0	0	1 8 +++++
Shell parakeet, <i>Melopsittacus undulatus</i>	1	++++	0	1 2 +++++
	2	++++	0	1 2 +++++
	3	++++	0	1 4 +++++
	4	++++	0	1 1 +++++,
				1 2 ++
	5*	++++	++++	1 128 +++++
	6*	++++	++	1 16 +++++
	7	++++	0	1 16 +++++
	8	++++	0	1 128 +++++
	9*	++++	0	1 2 +++++
	10*	0	0	1 1 +++++
	11*	++++	0	0
	12*	++++	0	1 1 +++++,
				1 2 +++
	13	++++	0	1 2 ++++

* Immature, all other parakeets and all cockatoos mature

sis in an aviary, barnyard or in an importation of tropical birds. All the evidence recently collected on 250 parakeets from suspected aviaries has proven the absence of infection by inoculation of the tissues, when a 10 per cent sample of the aviary yielded birds with negative complement fixation reactions. On the other hand, a shipment of psittacines or pigeons from a loft with over 1 or 2 per cent positive sera has invariably been proven by the mouse inoculation tests

grass parakeets or canary parrots In England and among bird fanciers the name Australian budgerigar (a corruption of 'Betcherrygah' the name the Australian aborigines call them meaning 'Pretty Bird') or shell parakeet is the most popular The colloquial designation 'love-bird' is misleading since this name is correctly applied to parrot-like birds (*Agapornis*) which originate from Africa The shell parakeets are found as native birds on the large grassy plains of Australia feeding on the flowers and seeds of the long grasses Their breeding places are chiefly in the southern parts but in the dry season when their food is scarce they emigrate northwards breeding in holes of decayed tree trunks into which they burrow like rats hundreds of pairs sometimes nesting in the same tree The wild budgerigars average from 7 to 8 inches long the rump is bright grass green and the back up to the crown of the head greenish black each feather being edged with bright yellow Sexes are distinguishable chiefly by the cere at the base of the upper mandible which in the male is always dark indigo blue after it is about 4 months old In the female the color is usually buff to brown at the height of the breeding season The hens lay on alternate days 4 to 6 white eggs (in captivity as many as 8 to 10) Incubation is about 20 days and since the hen commences to sit with the first egg there may be 10 to 12 days difference in the ages of the young The young budgerigars are not feathered and fit to leave the nest until they are at least 5 weeks old They are sexually mature when about 6-8 months old, the penciling disappears at that time and a yellow forehead is readily recognized The bird is then designated as being 'capped'

Importations to England and the United States were made as early as 1870 and from that time on the aviculturists have made it one of the most popular cage birds largely on account of the many attractive color varieties which can be created through cross-breeding A demand for these varieties which were formerly rarities and the prolific breeding habits and the hardiness of the species have made the shell parakeet the cage bird par excellence It is now being raised in every section of the United States where the breeding in captivity by 1925 has become a commercial enterprise largely on account of export restrictions imposed on the native birds by the Australian Commonwealth in 1920 In California production reached its peak in 1930 The stocks came from various sources mostly Japan It may be of interest to note that according to reliable reports occasionally the shipments were greatly decimated by 'septic fever' caused by overcrowding in dirty cages

The examination of shell parakeets for psittacosis infection was greatly facilitated by the early recognition that the young immature birds known as 'crawlers' doubtless the products of intensive in- and ex-breeding were particularly prone to suffer from psittacosis Sick parakeets of all ages are sometimes recognized by their behavior and appearance They show signs of sleepiness sit motionless on the perch with ruffled feathers and semiclosed or completely closed eyes and exhibit fits of shivering or convulsions A loss of weight with a protruding breastbone and labored breathing due to mucus at the nasal orifice is fairly common In a relatively small percentage there

TABLE 2

The Distribution of Spontaneous Psittacosis Infection in the Class Aves

Nomenclature according to J L Peter's Checklist of Birds of the World, I to IV, Cambridge, Massachusetts and Birds of British Museum, 1888, XII, London

Order Procellariiformes (1)

Family Procellariidae *Fulmarus glacialis*

Order Galliformes (1)

Family Phasianidae *Gallus gallus* (chicken varieties)

Order Columbiformes (1)

Sub-family Columbinæ *Columba livia livia* (pigeon varieties), *Streptopelia decaocto decaocto* and *Streptopelia semitorquata* ? (Doves)

Order Passeriformes (12)

Family Ploceidae

Sub-family Viduinae *Lagonosticta senegalensis* L (firefinch), *Munia oryzivora* (ricebirds), *Uroloncha striata* (Bengalese finch), *Poephila mirabilis*, *P. gouldiae* and *P. acuticauda* (Lady Gould finches), *Zonaeagnthus guttatus*

Family Fringillidae

Sub-family Fringillinae *Carduelis carduelis* and *C. major* L (gold finch), *Chrysomitris tristis* (gold finch), *Serinus canaria* (canary), *Pyrrhula europaea* (bullfinch), *Cyanospiza cyris* L (painted bunting)

Order Psittaciformes (19 genera and 31 species)

Family Psittacidae

Sub-family Lorinae

Genus Trichoglossus (*lorikeets*) *Tr. chlorolepidotus* (Kuhl), *Tr. haematodes moluccanus* (Gmelin)

Genus Kakatoe (cockatoos) *K. sanguinea* (blood-stained cockatoos), *K. galerita galerita* (Latham) (sulphur-crested cockatoos)

Sub-genus Eolophus (galah) *Kakatoe roseicapilla roseicapilla* (Vieillot) (pink parrot)

Genus Nymphicus *N. hollandicus* (Kerr) (quarrion, cockateel)

Sub-family Psittacinae

Genus Ara *A. macao* (macaws)

Genus Aratinga *A. pertinax tortugensis* (parakeet), *A. pertinax margaritensis*

Genus Nandayus *N. nanday* (Vieillot) (black-headed parrot)

Genus Forpus *F. passerinus Spengeli* (Hartland) (parrotlet), *F. conspicillatus conspicillatus* (Lafresnaye)

Genus Myiopsitta *M. monachus monachus* (Boddaert) (green parakeet)

Genus Graydidascalus *Gr. brachyurus* (Kuhl)

Genus Pionus *P. menstruus* (Linné) (blue-headed parrot)

Genus Amazona *A. festiva festiva* (L.), *A. barbadensis barbadensis* (Gmelin), *A. aestiva aestiva*, *A. ochrocephalus panamensis* (Panama yellow-headed parrot), *A. albifrons albifrons* (spectacled parrot)

Genus Psittacus *Psittacus erithacus erithacus* (Linné) (Senegambian love-bird)

Genus Psittacula *Ps. krameri manillensis* (Beckstein) (parrotlet)

Genus Polytelis *P. anthopeplus* (Lear) (regent parrot)

Genus Alisterus *A. scapularis* (king parrot)

Genus Agapornis *A. roseicollis* (Vieillot), *A. personata* (Reichenow) (African love-birds)

Genus Platycercus (Rosella) *Pl. elegans elegans* (crimson parrot) (Gmelin), *Pl. eximius eximius* (Shaw), *P. zonarius semitorquatus* (Quoy and Gaimard), *Pl. adiscitus*, *Pl. eximius ceciliae*

Genus Psephotus *Ps. haematonotus* (Gould) (grass parrot)

Genus Melopsittacus *M. undulatus* (Shaw) (budgerigars, parakeets)

the immature birds with moderately enlarged spleens carry the virus more frequently than the old parakeets. For example in an aviary 48 per cent of the immature and 8 per cent of the mature parakeets harbored the virus. Further it became apparent that the birds contract their psittacosis infection very early in life, even in the nest or congenitally. At least in 3 parakeets the ovaries and in another the yolk of the egg found in the oviduct carried a weak virus. The *Microbacterium* leaves the body of the shell parakeets and, as a matter of fact, of parrots and of parrotlets by way of the cloaca and the nasal mucus. In the acute stage both routes of elimination may simultaneously function although individuals may be encountered in which no virus elimination can be demonstrated. The cloacal content is highly infectious when the birds exhibit signs of diarrhoea and polyuria. Since the kidneys are rich in virus and the small intestines and colon are not it is reasonable to suspect that the urine is the vehicle for the virus. Parakeets with latent infections if not in the incubationary stage eliminate the virus in small amounts; consequently they are less dangerous than acutely ill birds which contaminate the environment with highly infectious fecal material.

Experimental infections have proven the great susceptibility of immature shell parakeets but they have furthermore shown that the infections with massive doses are not always fatal. Certain non-infected aviaries furnished parakeets which upon injection with one million fatal mouse doses yielded only 10-15 per cent deaths and 40 per cent carriers. This native innate resistance is probably of genetic origin; it is certainly not conditioned by demonstrable antibodies but such birds are capable of destroying large amounts of virus within less than 3 weeks. In mature parakeets raised in non-infected aviaries the liability to fatal infections may entirely disappear but the susceptibility remains constant and approximately 50 per cent carriers develop as a sequel to the inoculation of the virus. Latency has been proven for at least 355 days; it may doubtless be longer in individual parakeets although the majority will free their organs within 2 to 14 months. Immature and mature budgerigars from infected aviaries acquire more rapidly a sterile immunity than those from non-infected premises. It is reasonable to presume that the birds which have been infected in the nest are partially immune to re-infection; thus they will offer the virus merely temporary lodging for multiplication but aid in the re-establishment of the infection chain. In fact in infected aviaries, parakeets which harbor the virus in the nares (probably inhaled) or in the intestinal content (ingestion of soiled seeds) without infectious organs have repeatedly been encountered.

An infection which is so *eminently latent* has a variable incubation time. The interval between injection and death varies between 5 and 93 days (Meyer), in exposure tests of healthy parakeets to carriers in a cage the onset of symptoms was on the 65th and death on the 75th in another bird on the 95th and death on the 103th day of the contact period. Ten of 17 parakeets exposed presented on the 98th day lesions of psittacosis and the virus was demonstrated in the spleen of 8. Other experiments suggest that these inapparent infections

may be diarrhoea with greenish stools or more often soiled tail feathers with grayish, mortar-like urate concretions. Birds may remain in this stage for several days and then die suddenly or make a slow recovery. Signs of this sort are not typical for psittacosis, *the autopsy and the laboratory tests are all important in order to determine the cause of the illness*. A parakeet dead or acutely ill, or recently recovered from an attack of psittacosis, shows at postmortem a few drops of mucus on the ceres, atrophic pectoral muscles, a large, heavy, tough, slightly saffron to ochre colored liver, occasionally (in about 10 per cent) studded with fresh or partially healed necroses and infarcts, a slightly enlarged and congested spleen, very rarely a few consolidated patches of pneumonia in the lower portions of one or both lobes of the lungs. The M M P bodies may be readily seen in smears or by inoculations into mice, the "virus" may be demonstrated in every organ, even the blood. The cultures prepared from the tissues, as a rule, are sterile on lifeless media. Histologic examination of the various organ structures reveals proliferation and destruction of the reticulo-endothelial system in the liver and the spleen, the main centers of multiplication of the virus, enormous numbers of monocytes are usually present in the spleen. In the kidneys, the tubular epithelial cells, the glomerular capsular epithelial cells and the densely infiltrated interstitial spaces between the tubules are likewise the site of growth of the *Microbacterium multiforme psittacosis*.

In the early stages of the studies, the visibly healthy, well-nourished shell parakeets with essentially negative autopsy findings, except a slightly or definitely enlarged spleen, became increasingly more important when it was proven that the splenic and hepatic emulsions on inoculation into mice produced psittacosis. These *latent, inapparent* virus infections represent the corner stone of the entire psittacosis and ornithosis problem. On their recognition rests the present-day control measures. To detect in an aviary the presence of psittacosis by looking for sick shell parakeets is of little value, but the autopsy of a 10 to 20 per cent sample and the testing of the organ pools on mice has furnished conclusive evidence on which quarantine, and ultimately destruction, may be enforced. Thus in the course of the past 10 years the Hooper Foundation autopsied and tested 7,560 and the California State Department of Public Health (Miss D. Beck) examined 19,280 or a total of 26,842 shell parakeets. This extensive experience has taught that the degree of latent psittacosis may be predicted by the percentage of spleens exceeding in diameter the normal average of 1 to 2 mm. However, it must be mentioned that not every enlarged spleen is infectious, or that birds with grossly normal spleens may not be infected. Spleens over 7 mm. may be free from virus, but 2-3 year old parakeets with myeloma-like spleens (23-24 mm. diameter) may carry the virus not only in the spleen but in the liver as well. Microscopic examinations of organ smears rarely, if ever, show typical virus particles, but certain small intracellular acidophilic discs have assumed some diagnostic significance.

The percentage of virus-carrying birds in a pen or in an entire aviary was determined by autopsies and inoculation tests of the organs of individual birds, it varied a few years ago from 10 to 90 per cent. In general, it was proven that

forme psittacosis is present in large numbers, free or in monocytic cells. In the few pigeons in which pneumonic patches were demonstrated, the *Salmonella* organisms were invariably isolated from the lesions. Latent infections are characterized by enlarged dark purplish mottled or pale spleens and soft grayish kidneys. Organ emulsions from such birds produce on intraperitoneal injection into mice definitely enlarged spleens without definite findings of elementary bodies. Suspensions of such spleens induce in mice on nasal administration focal or lobular, rarely fatal pneumonias, and on intracranial injection a fatal choromeningitis with an enormous number of M M P bodies. Even continuous passage through mice fails to enhance the infectivity for this rodent, despite the fact that the virus may be highly pathogenic for ricebirds and parrakeets. As a whole, there are considerable variations in the infectivity even for doves (*Streptopelia risoria*) which, as a rule, are free from ornithosis. Some strains readily infect by the intramuscular route, all are pathogenic on intracranial administration. On the other hand, pigeons (*Columba* varieties) which appear healthy and show no complement fixing antibodies against "psittacosis" may carry the virus in their tissues, it is thus not surprising to find such birds immune to intramuscular infections. No clinical manifestations are noted, but antibodies appear promptly in the blood sera. A few may succumb to massive intracranial infections. Until a method has been developed to detect latent ornithosis infections in pigeons, the experimental study of the host-parasite relationship cannot be undertaken with any degree of success. At least for the present, the remarkable resistance to feeding or intramuscular injection of pigeons to virus, already noted by Bedson and Western, is in all probability attributable to an acquired immunity, frequently conditioned by the persistence of the infective agent in the tissues. How the virus escapes from the pigeon host is not definitely known. Tests completed to date indicate that the cloacal content harbors the infective agent in such low concentrations that the relatively non-susceptible mouse fails to react. However, the demonstration of the virus in the kidneys would justify the belief that the urine is infectious, and as an admixture to the cloacal content maintains the infection chain. Finally it should be noted that parrakeet psittacosis viruses, even on intracerebral injection, fail to produce fatal infections in pigeons (Pinkerton and Henderson), but occasionally doves appear susceptible (Meyer and Eddie). However, the so-called meningopneumonitis virus of Francis and Magill behaves like a pigeon virus. It is fatal to doves on intracranial and to ricebirds and parrakeets on intramuscular injection.

The susceptibility of chickens to the "psittacosis" virus was anticipated by the successful infection experiments of Bedson and Western, Krumwiede et alia, Levinthal, Dahmen and Hamet. Exposure experiments of 10 young chickens in pens in which sick parrakeets or those with latent infections (40 per cent) were held yielded two fatal (on the 52nd and 63rd day of the exposure period) and four latent infections with typical lesions of splenic tumor and liver necrosis (Meyer). It is therefore not surprising that recently a chicken farm in New Jersey on which a human case of psittacosis had been seen yielded at least 3 emaciated chickens harboring a psittacosis-like virus in the spleen, liver

may have occurred within the first 20 days after exposure. These and many more observations leave no doubt that in order to detect the development of acute fatal avian psittacosis in a shipment, the quarantine period must be extended to 6 months. This policy has in recent years been followed by the United States Public Health Service for the importation of psittacine birds.

Less detailed observations on South American parrots, parrotlets, Australian cockateels and cockatoos have, in general, disclosed an identical parasitism of the psittacosis virus involving anatomically in the acute disease the pericardium and the air sacs. Demonstrable infection, however, may be rare, but enlarged non-infective spleens are probably indicative of past infections. Noteworthy, however, is the fact that the viruses isolated from the Australian parakeets and parrots never achieve the mouse infectivity of the classical strains obtained from North American or Latin American sources (Meyer and Eddie, Burnet, Treman). African parrot-like birds, such as "peached faced" or "masked" love-birds (*Agapornis* varieties), raised in California are apparently quite resistant to infection. Spontaneous acute or latent infections, despite heavy exposure in infected aviaries, are rare and experimental reproduction of the disease succeeds only with difficulty. Thus, it is not surprising that these birds have been involved only once in a human outbreak (New Jersey, 1940).

III THE VIRUS PARASITISM IN FINCHES AND CANARIES

In the group of the thrushes and finches, the susceptibility of the Java rice-bird (*Munia oryzivora*) and the canary is very high. Ninety to 95 per cent succumb to exposure or inoculations in from 5 to 65 days. Small inocula may cause clinical disease followed by recovery and latency of the virus for a period of 6 weeks. But since the cloaca rarely contains the virus in demonstrable amounts, no provisions for transmission to new hosts have been perfected. Exposure of susceptible birds to virus-carrying ricebirds or canaries has never resulted in infection. In fact, canaries have never caused air-borne infections, intimate contact, the handling of dead or "doctoring" of sick birds has been reported as the cause, as might be expected in the light of these observations. The finches are aberrant hosts which acquire (Elkeles and Barros, Meyer and Eddie) their infection, as a rule, from exposure to diseased parakeets or parrots held in the same room or aviary, or through seeds contaminated by the droppings of these species (Gerlach).

IV THE PARASITISM OF THE ORNITHOSIS VIRUS IN PIGEONS, CHICKENS AND FULMARS

The host relationship of the various psittacosis-like viruses, which have recently been isolated from pigeons, is in the course of a detailed study. The acute infections thus far seen may in reality be relapses (Pinkerton and Swank, Meyer and Eddie). In a number of instances, the virus infections of pigeons are complicated by a simultaneous presence of *S. typhi murium*. At autopsy, plastic exudates on the pericardium and over the enlarged liver, with and without necrosis, and enlarged spleens attract attention. The *Microbacterium multi-*

forme psittacosis is present in large numbers, free or in monocytic cells. In the few pigeons in which pneumonic patches were demonstrated, the *Salmonella* organisms were invariably isolated from the lesions. Latent infections are characterized by enlarged dark purplish mottled or pale spleens and soft grayish kidneys. Organ emulsions from such birds produce on intraperitoneal injection into mice definitely enlarged spleens without definite findings of elementary bodies. Suspensions of such spleens induce in mice on nasal administration focal or lobular, rarely fatal pneumonias, and on intracranial injection a fatal chorion meningitis with an enormous number of M M P bodies. Even continuous passage through mice fails to enhance the infectivity for this rodent, despite the fact that the virus may be highly pathogenic for micebirds and parakeets. As a whole, there are considerable variations in the infectivity even for doves (*Streptopelia risoria*) which, as a rule, are free from ornithosis. Some strains readily infect by the intramuscular route, all are pathogenic on intracranial administration. On the other hand, pigeons (*Columba* varieties) which appear healthy and show no complement fixing antibodies against "psittacosis" may carry the virus in their tissues, it is thus not surprising to find such birds immune to intramuscular infections. No clinical manifestations are noted, but antibodies appear promptly in the blood sera. A few may succumb to massive intracranial infections. Until a method has been developed to detect latent ornithosis infections in pigeons, the experimental study of the host-parasite relationship cannot be undertaken with any degree of success. At least for the present, the remarkable resistance to feeding or intramuscular injection of pigeons to virus, already noted by Bedson and Western, is in all probability attributable to an acquired immunity, frequently conditioned by the persistence of the infective agent in the tissues. How the virus escapes from the pigeon host is not definitely known. Tests completed to date indicate that the cloacal content harbors the infective agent in such low concentrations that the relatively non-susceptible mouse fails to react. However, the demonstration of the virus in the kidneys would justify the belief that the urine is infectious, and as an admixture to the cloacal content maintains the infection chain. Finally, it should be noted that parakeet psittacosis viruses, even on intracerebral injection, fail to produce fatal infections in pigeons (Pinkerton and Henderson), but occasionally doves appear susceptible (Meyer and Eddie). However, the so-called meningopneumonitis virus of Francis and Magill behaves like a pigeon virus. It is fatal to doves on intracranial and to micebirds and parakeets on intramuscular injection.

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and kidneys This infective agent, only partly studied, resembles in general the pigeon viruses, it infects young chickens, pigeons, doves, parakeets and ricebirds on intracranial and intramuscular injection The primary isolation of the virus is quite difficult, and since the complement fixation test in its present technical development has failed, the extent of the disease in barn yards, the host-parasite relationship and the interrelation between acute and latent infection are still unknown

The examination of 272 fulmar petrels (*Fulmarus glacialis*) from the Faroe Islands by Haagen and Mauer has proven in these sea birds the existence of a psittacosis virus, which is transmissible to mice and parakeets An identical virus was obtained from materials coming from human cases Only newly fledged fulmar petrels, which leave their nests and collect on the rocks where they are gathered by the men, are infected Whether acute or merely latent infections occur has not been determined According to a recent report by Bedson, the sera of five cases of a similar human disease sent to him from Iceland where fulmar petrels are used as food, all gave positive psittacosis complement fixation tests Thus, the whole migration and breeding range of these sea birds must now be considered a potential reservoir of ornithosis One naturally wonders whether other species of sea birds may not suffer from a similar infection This possibility is the subject of further inquiry and investigation

All the information relative to ornithosis, at present available, attests to the remarkable tendency to latency of the avian infection in every species of bird, except those which are apparently aberrant hosts like the finches and thrushes Moreover, the infection is acquired in the nests or at least in youth Recovery from this early contact with the parasite ensures a life-long relative resistance However, since it is frequently associated with latency, the *balance of the immunity may become disturbed in favor of the virus* With experimentally infected shell parakeets (Meyer and Eddie), cockatoos brought from the bush (Burnet and MacNamara) or pigeons brought from lofts and held in the laboratory, crowding in poorly lighted, insanitary cages activates the virus which is lying dormant in the spleen or liver or kidneys, intensive multiplication ensues, and relapses and even deaths of mature birds are the sequel That improper feeding may mobilize a latent infection, in particular, that a thiamin-deficient diet may activate it, is beautifully illustrated by the observations of Pinkerton and Swank, who, in the course of their experiments, found 5 per cent of the pigeons of a certain establishment to develop apparent infections in the form of paralysis In order to estimate the extent of latent ornithosis in the form of paralysis particular loft, the sera of 12 were tested and 6 gave definite reactions As already indicated, a negative serum test does not preclude virus latency Hence, the actual percentage of infected pigeons is probably much higher In fact, this deduction has been recently proven by tests made with sera of pigeons from the same loft after the birds had been used in certain biological tests, which stimulated the reticulo-endothelial system Not less than 90 per cent of the sera gave an anamnestic fixation reaction indicative of a previous contact with the ornithotic virus In the epidemiology of human psittacosis, the relapses

in birds doubtless play an important rôle. The transplantation of tropical birds or pigeons to a cooler climate and held under unfavorable environmental conditions may disturb the balanced immunity to such an extent that the subsequent multiplication of the virus may convert the animal into a shedder dangerous to its owner, or to the susceptible mates which may develop acute psittacosis. The recent outbreak of psittacosis at the National Zoological Park at Washington (Tomlinson) is most likely attributable to a set of circumstances which followed a breakdown of the heating system in the bird house. It occurred about a week before the first appearance of psittacosis among the birds, which had been under observation for many months, and had shown no illness. Since Amazon parrots are frequently carriers of virus for long periods—in one of the author's observation for at least 523 days—it is probably correct to suspect the chilling as a factor in converting one or several of these birds into active shedders.

V PSITTACOSIS IN WILD PARROTS

There is no dearth of speculative thoughts relative to the ultimate origin of the parrot infections responsible for the pandemic of 1929-1930. An enzootic disease among the native parrots of South America was suspected, but since human cases had not been reported, despite the fact that every household possessed pet birds, and, furthermore, since the studies of Pacheco and Bier had failed to demonstrate the psittacotic virus in Brazilian parrots from which they merely isolated *Salmonella* varieties, such a possibility was dismissed as quite unlikely. These early conclusions have, however, been seriously questioned in view of the examinations of shipments of parrotlets, conures, parrots and macaws, which during the past 8 years reached the Quarantine Stations of California. In 1933, several Spengel's parrotlets (*Forpus passerinus*) and conures from Colombia were proven to be carriers of an active psittacotic virus. Since they had been held in captivity, infection was not necessarily present in the jungle birds. But in 1938 two other shipments from Colombia, one with acutely infected Amazon parrots and macaws, brought 73 parrotlets of which 15 had enlarged spleens and yielded the psittacotic virus. According to reliable information, the second shipment had not been held in captivity for any length of time, hence, it is quite certain that enzootic psittacosis exists in the neotropical regions of South America, and suspicion is cast on the parrotlets as the primary reservoirs. According to M. Menk (see Elkeles and Barros), folklore stories connect a disease of man "pajaroazul" (an influenza-like malady) with exposure or intimate contact with "blue" birds, or more correctly, parrots. These possibilities deserve further local investigation. The position of the principal parrots of trade, the Amazon varieties, is problematical, the only birds which have recently been examined were the Panama yellow headed parrots imported through Mexico. On two occasions, they were connected with human infections and the birds were either carriers or had died acutely from psittacosis. There is considerable indirect evidence that these parrots are spontaneously infected in the forests of South and Central America.

In denying the existence of enzootic parrot psittacosis in the wild, the observations by Burnet are frequently overlooked. As a rule, it takes the form of a latent infection, producing no visible symptoms or any pathological signs beyond an enlarged spleen. The universal distribution of the infection involving birds of two distinct families, one of which is the Lorinae with the three genera *Trichoglossus* (lorikeet), *Kakatoe* (cockatoo) and *Nymphicus* (cockateel), which are restricted to the Australian region, and the mildness of the infection make it reasonably certain that the enzootic state has been present in Australia for centuries, at least. Moreover, since the Australian continent can be regarded as the main center of parrot evolution, it is quite possible that it was present for all the geological period during which the psittacine families assumed their ascendancy. Burnet, in discussing the relationship between the virus and the host, believes that the standard is probably as follows: "The young birds are infected with the virus in the nest, suffering a mild infection, any symptoms having disappeared by the time they are ready to fly. The virus, however, persists in spleen and kidney, at least until the next breeding season, and is then available to infect the new generation of birds. It is reasonable to presume that birds which have been infected in the nests will be immune to re-infection from other sources. Variations from this standard condition may favor either host or parasites. In the first place, the proportion of infected birds varies from species to species, and also in different batches of birds of the same species. Indirect evidence that many parrots escape nest infection is also obtained from the occurrence of numerous fatal infections that sometimes follow the introduction of infected birds. In one of the Australian Zoological Gardens a high mortality amongst several species followed the addition of a few *Barnardius* parrots from Western Australia to the aviary concerned."

In 1939 Burnet obtained evidence that the balance was disturbed in favor of the virus. In at least three states, a notable number of deaths of wild parrots occurred in the bush. In Victoria, dead King parrots and crimson rosellas with acute signs of psittacosis were picked up. Much more extensive mortalities occurred in the Southeastern districts of South Australia, the birds, probably grass parrots (*Psephotus* and *Neophema*), dying in such numbers that the occurrence was noted in the daily press. These widespread epizootics in 1938 await an explanation through careful surveys with respect to population density of the different species, regional food scarcity and consequent migration. The psittacotic virus strains isolated from this epizootic possessed no unusual characteristics. It is not unlikely that this epizootic state among the Australian parrots was intimately connected with the very heavy psittacosis infection, which was encountered by Meyer and Eddie (1939) in an importation of King parrots, rosellas and cockateels intended for the Australian Pavilion at the Golden Gate International Exposition.

Although the evidence, as yet fragmentary, strongly incriminates psittacosis as an almost universal low-grade infection of parrots, not merely confined to the Australian region, with as many species as in the other five zoogeographical regions combined, Pintero Garcia in a recent review of the origin of the disease

in Argentina reaches the interesting conclusion that psittacosis is an importation. In particular, he suspects the Australian parrakeets as the reservoir to which all the evil may ultimately be traced. This interpretation ignores the facts presented by the examination of at least three importations from South America, and the outbreak of psittacosis at the London Zoological Gardens (Troup Adam and Bedson), and possibly the National Zoological Park at Washington which strongly incriminate the neotropical region as an enzootic reservoir for a low-grade avian psittacosis as a population regulator, which only on rare occasions flares up into the dramatically infective disease as seen in the exhibition rooms of Córdoba and Tucumán.

VI PSITTACOSIS IN COMMERCIAL PARRAKEET BREEDING ESTABLISHMENTS

By 1932 the commercial breeding establishments and aviaries of California were and recently those of Florida and Texas are now enzootic foci of avian psittacosis. The extent of these infections is conclusively established by the

TABLE 3
Examination of California Aviaries

	1922	1933	1934	1935	1936	1937	1938	1939	1940	1941
Aviaries with infected parrakeets	27 (100)*	23 (44.2)	47 (23.9)	4 (3.7)	1 (2.7)	1 (3.8)	3 (16.6)		1 (7.6)	8 (6.3)
Aviaries with non-infected parrakeets		29	136	109	38	26	18	13	12	126
Aviaries with anatomically suspicious parrakeets			12		8	6				1
Aviaries with inconclusive findings			1	18	5					3
Total aviaries tested	27	52	196	131	52	33	21	13	13	138

* Figures in parentheses indicate percentages

routine examinations conducted by the California State Department of Public Health in connection with the regular official control activities. They are summarized in Table 3.

In the spring of 1932 every establishment examined housed parrakeets with latent and some with acute psittacosis. With the destruction of close to 25 000 birds in 1934 the incidence was reduced below 10 per cent, and it is anticipated that the annual re-tests will permanently maintain the aviaries free from infection. Acute psittacosis has become a rarity, except on the premises of a large dealer who promiscuously mixed shell parrakeets with imported South American and Australian parrots. In 1940, in a sample of 271 parrakeets 197 presented enlarged spleens and several pools of these organs yielded the specific virus. The probability that this establishment had become re-infected and then distributed birds, which were responsible for human infection, was greatly fortified by two facts: (a) The breeding aviaries furnishing parrakeets to the dealer were proven free from psittacosis by several tests made at the same, but the

infection was found at the bird exchange (b) Not less than 37 per cent of the budgerigars harbored *S typhi murium* in the intestines and the spleens The same organism accompanied the virus present in the large parrots held on the premises It is a well known fact that shell parakeets raised in California are not carriers of Salmonellosis, but South American birds are frequently the hosts of these bacteria Since the virus was exchanged with the droppings, a simultaneous transfer of the Salmonella took place

A survey of different pens or entire aviaries in which every bird was examined and individually tested for virus on mice showed that within the flock the following categories of birds may be found (a) With typical psittacosis, (b) atypical cases, (c) with latent infections as closed carriers or shedders, (d) immune and uninfected, and (e) susceptible and uninfected By exposing ricebirds to suspected shedders, it was found that many of the infective parakeets became closed carriers after 60 to 80 days In fact, in an aviary consisting of 2,000 parakeets kept under observation and in which breeding operations were stopped by separation of the sexes, psittacosis as a cause of death disappeared entirely at the end of 2 months Latent infection was still present in the flock only to re-appear within 5 weeks after mating and breeding was resumed It is reasonable to suspect that the latent infections were transformed into shedder stages by the activities incident to egg laying, etc At first young parakeets and later even a few of the older birds, which had apparently escaped infection, died with typical lesions of acute psittacosis Hence, the standard parasite-host relationship as hypothesized by Burnet for the parrots in the wild state is proven for the Australian shell parakeet bred and raised in captivity Nest infections are rarely fatal, but in the past they have been common in some aviaries Persistence of the virus until the next breeding season assures the continuity of the infection chain Variations from this standard, which may favor either host or parasite, are just as common in the breeding establishments as in the bush For example, the introduction of infected parakeets in an aviary with a low latent infection rate indicative of a low rate of nest infections may be followed by a high mortality Crowding under poor sanitary conditions and intensive breeding favors the parasite In fact, in some aviaries the infectivity of the virus was maintained at very high level judged by the incidence of acute psittacosis created by many susceptibles through careless inbreeding Such dangerous reservoirs must be eliminated by the destruction of the entire flock Canadian aviaries, that had depended on their breeding stocks from California or Great Britain, are invariably housed indoors, in some instances in the basements of the houses This close proximity to the inhabitants has been responsible for a number of interesting epidemiologic situations (McNabb—personal communication) The incidence of latent infection as determined by individual tests of 128 parakeets was as high as 56.4 per cent, and is largely responsible for the 21 human cases which occurred among the bird fanciers and their clientele Another factor, namely the sale of very young parakeets not more than 4 to 6 weeks old, probably in the stage of shedding virus following their nest infection, and the habit of the owners to train such birds for resting

on their fingers, in consequence creating intimate contact, served as contributory causes to the frequent human infections

VII ORNITHOSIS IN THE PIGEON LOFTS

Since the beginning of 1941, the epidemiologic relationship between human cases of psittacosis and homing pigeons has shifted the interest to the pigeon lofts as reservoir of the virus. Attention was called to these breeding establishments or the back yard lofts used to house racing pigeons by two facts: (1) The serological examination of the blood sera of 30 pigeons owned by the son of a fatal case of psittacosis produced 19 or 63 per cent specific complement fixation reactions in dilutions of 1:32 and higher. (2) In the search for pigeons suitable for laboratory experimentation with psittacotic viruses, three lofts located in the San Francisco Bay area were sampled, each supplied a variable percentage of reactors except one, from which the dozen squabs tested proved negative. In rapid succession, pigeon lofts from the surroundings of Los Angeles, Visalia, Pasadena and Iowa furnished birds whose sera gave specific reactions with the psittacotic antigen. In connection with the epidemiologic investigation of two cases of human psittacosis in a mother and daughter, who had handled a sick pigeon in the heart of New York (referred to the Foundation through the courtesy of Dr. George S. Mirick, Hospital of the Rockefeller Institute) the sera of 30 pigeons caught in Central Park and kindly sent by the New York City Department of Health were serologically tested. Fifteen (50 per cent) gave specific reactions in serum dilutions from 1:8 and higher. Finally, a sample of 12 young pigeons from South Carolina which was obtained from the dealer who had supplied the pigeons used by Dr. Henry Pinkerton and Dr. R. L. Swank, was found to contain reactors. Although inoculation tests on doves (*Streptopelia risoria*) and a few pigeons (*Columba livia*) had proven the important fact that complement fixing antibodies appear promptly following the injection of parakeet or human psittacotic viruses, and that the infective agent was demonstrable in the kidneys as late as the 41st day, it became imperative to attempt the isolation of the infective agent responsible for the reactions in the pigeons. By special mouse passage tests, morphologically and culturally identical psittacosis viruses have been isolated from 17 pigeons from 7 different lofts or flocks located in California, New York and South Carolina. The data which appear important in this connection are listed in Table 4.

At first, it was believed that the virus could most readily be isolated from the enlarged spleens, which varied in length from 12 to 27 mm. of pigeons with specific antibodies. However, it was soon found through tests of non-reactors with splenic tumors or slightly enlarged kidneys that the virus could likewise be discovered in the organs by repeated mouse passages. In fact the data collected to date suggest approximately the following state of affairs. In acutely sick pigeons, the virus is *morphologically* demonstrable in the pericardial or peritoneal exudates, it may be transferred to mice by intracerebral injections, provided the test material is free from *S. typhi murum*. The chorionmeningitis, which is induced by these injections, is fatal in a large percentage of mice and

infection was found at the bird exchange (b) Not less than 37 per cent of the budgerigars harbored *S typhi murium* in the intestines and the spleens The same organism accompanied the virus present in the large parrots held on the premises It is a well known fact that shell parakeets raised in California are not carriers of Salmonellosis, but South American birds are frequently the hosts of these bacteria Since the virus was exchanged with the droppings, a simultaneous transfer of the *Salmonella* took place

A survey of different pens or entire aviaries in which every bird was examined and individually tested for virus on mice showed that within the flock the following categories of birds may be found (a) With typical psittacosis, (b) atypical cases, (c) with latent infections as closed carriers or shedders, (d) immune and uninfected, and (e) susceptible and uninfected By exposing ricebirds to suspected shedders, it was found that many of the infective parakeets became closed carriers after 60 to 80 days In fact, in an aviary consisting of 2,000 parakeets kept under observation and in which breeding operations were stopped by separation of the sexes, psittacosis as a cause of death disappeared entirely at the end of 2 months Latent infection was still present in the flock only to re-appear within 5 weeks after mating and breeding was resumed It is reasonable to suspect that the latent infections were transformed into shedder stages by the activities incident to egg laying, etc At first young parakeets and later even a few of the older birds, which had apparently escaped infection, died with typical lesions of acute psittacosis Hence, the standard parasite-host relationship as hypothesized by Burnet for the parrots in the wild state is proven for the Australian shell parakeet bred and raised in captivity Nest infections are rarely fatal, but in the past they have been common in some aviaries Persistence of the virus until the next breeding season assures the continuity of the infection chain Variations from this standard, which may favor either host or parasite, are just as common in the breeding establishments as in the bush For example, the introduction of infected parakeets in an aviary with a low latent infection rate indicative of a low rate of nest infections may be followed by a high mortality Crowding under poor sanitary conditions and intensive breeding favors the parasite In fact, in some aviaries the infectivity of the virus was maintained at very high level judged by the incidence of acute psittacosis created by many susceptibles through careless inbreeding Such dangerous reservoirs must be eliminated by the destruction of the entire flock Canadian aviaries, that had depended on their breeding stocks from California or Great Britain, are invariably housed indoors, in some instances in the basements of the houses This close proximity to the inhabitants has been responsible for a number of interesting epidemiologic situations (McNabb—personal communication) The incidence of latent infection as determined by individual tests of 128 parakeets was as high as 56.4 per cent, and is largely responsible for the 21 human cases which occurred among the bird fanciers and their clientele Another factor, namely the sale of very young parakeets not more than 4 to 6 weeks old, probably in the stage of shedding virus following their nest infection, and the habit of the owners to train such birds for resting

the abundance of *Microbacterium multifforme psittacosis* in all its development stages is diagnostically significant. Pigeons with antibodies may present the residuals of a passed infection and both the liver and spleen may be swollen and enlarged. Organ emulsions inoculated intraperitoneally may produce no visible illness but at autopsy on the 20th day the enlarged spleens with indefinite microscopic findings attract attention. Subinoculations of splenic suspensions intracerebrally may cause the development of virus meningitis. As many as 60 per cent of the non-reacting pigeons will yield the virus from the enlarged spleen, or the grossly normal kidneys or both, by a primary enrichment in the mouse spleen and final demonstration in the meninges. Some of the pigeon viruses have been passed intraperitoneally through mice, an occasional rodent may succumb, the abdominal cavity is filled with a seropurulent exudate, and a few liver necroses and an enlarged spleen are found. Freshly isolated strains on intranasal administration may produce non-fatal focal or lobular consolidations scattered through the lungs. Only when the pathogenicity for the mice has been enhanced through passage may fatal pulmonary infections be induced. Attempts to find the virus in the droppings have not been successful, since the emulsions had to be filtered or injected subcutaneously. Exposure experiments in placing very susceptible ricebirds in cages with pigeons are in progress. All the evidence to date suggests that an ornithotic infection due to a virus of low mouse infectivity and pathogenicity is widely distributed through the pigeon lofts of this country. With respect to the mouse reactions, the viruses resemble those isolated from Australian parrakeets or cockatoos. Since the psittacotic strains are highly adapted to their hosts, one is justified in suspecting that the pigeon strains are equally symbiotic in avian tissues, and not readily transferable to aberrant mammalian hosts. This has been proven by the ease with which these viruses infect doves (fortunately some have been found free from psittacosis), parrakeets and rice-birds. The low invasiveness and pathogenicity possessed by the majority of strains obtained from pigeons, and as a matter of fact the viruses obtained from chickens on one poultry farm are, in all probability conditioned by several factors. Human infections are probably infrequent for the following reasons: (a) The virus is rarely discharged in large enough amounts to establish the infection chain, except when the pigeons are ill. The epidemiological histories of the proven human infections invariably report the handling of sick pigeons, or the flock or cage to which the patients were exposed included clinically and anatomically diseased birds at the time of exposure or shortly before. (b) Viruses of such low pathogenicity rarely cause frank human infections. Despite the tremendous reservoir of psittacosis in Australia the actual number of human cases is less than one dozen with only one death. That these viruses may be responsible for influenza-like, mild atypical and short-lived infections is suggested by the appearance of complement fixing antibodies for the psittacosis antigen in the sera of persons who were exposed to sick pigeons. Furthermore the few tests thus far made on owners of pigeon lofts, who give positive complement fixation reactions but no history of illness comparable with psittacosis, indicate frequent subclinical infections. On the

TABLE 4
Complement Fixation Reactions and Isolation of Virus from Pigeons

CALIFORNIA										U S A				
San I candro	Hayward		Hayward K L	Pasadena Br		El Monte		Visalia	Pasadena A	South Carolina	New York City	Iowa		
	Old	Young		Old	Female	Young	Old					Old	Farm A	Farm B
0	0	12	0	8	4	2	4	0	0	0	10	8	2	0
12	0		1	1		1					5	1		1
18	0		1			1					3			
10	0		1			1					3			
32	1		1	2		1			2	3	3	1		
64	1		1						2	1	4	3		
128	2		2	4	2		2			1	2			1
1 250	1		1	1						1	3			
Total	12	12	12	10	14	10	6	0	13	12	30	13	2	8
Percentage of reactors	50%	0	50%	50%	78%	50%	33%	33%	44%	50%	50%	30%		10%
Isolation of virus (10 pigeons)	Not at tempted	(1) 7708, spleen 15 x 8 (2) P P, peri cardial oxidato	Not at tempted	(1) P 1029, male spleen 12 x 4, C F, 1 32 (2) P 1871, male spleen 28 x 9, C F, 1 04 (3) P 1835, fe male spleen 10 x 17 (4) P 1808, female spleen 8 x 8, C F, 0 (5) P 1808, fe male spleen 12 x 6, C F, 0 (6) 345 spleen 20 x 9, C I, 1 04	(1) No 1-000, female spleen 25 x 10, C I, 0 (2) 7812, female spleen 10 x 17 (3) 7824, female spleen 8 x 8, C F, 0 (4) 50 spleen 17 x 8, C F, 1 128 +++++	(1) 51, spleen 18 x 7, C F, 0 (2) 55, spleen 18 x 8, C F, 0 (3) P 57, spleen 12 x 7, C F, 0 (4) 50 spleen 17 x 8, C F, 1 128 +++++	(1) 48, spleen 20 x 7, C F, 0 44%	(1) 38, spleen 16 x 7, C F, 0 50%	(1) 28, C I, 1 32 +++++ (2) 15, C I, 1 04 (3) 22, C F, 1 128 +++++	Not tested				

infections. Until 1931 the breeders were unaware of the existence of this disease among their breeding stock. Greed for greater returns, lack of knowledge concerning certain fundamental laws on inbreeding combined with insanitary conditions, and the desire to dispose of very young immature birds as quickly as possible dispersed through the trade many acutely ill parakeets and carriers. Brought to the pet shops they were quickly sold only to die in the homes of the purchasers or they infected canaries or even macaws (Pittsburg outbreak) thus scattering disease and death through various secondary channels. Equally important has been the general attitude towards psittacosis. Bird breeders, pet shop owners, aviculturists and lovers of birds, even veterinarians doubted the existence of the disease. Until the identical infective agent was demonstrated in the blood and sputum of the patients and the organs of psittacine birds the diagnosis of parrot fever and the mutual relationship between the apparently healthy parakeet and the typhoid pneumonia of his owner was subject to various but incorrect interpretations by the prejudiced laity. That persons engaged in the breeding, raising, transportation and sale of psittacine birds are particularly liable to psittacosis was not accepted though published records amply attested to their existence. Notwithstanding the reports by Widowitz (Graz 1929), Roch and Wohlers (Genera 1929), Prausnitz and Stepp (Breslau 1932), Gerlach (1936), McNabb (Canada 1940-1941) of the occurrence of psittacosis among bird breeders by Marion and Dubois (1892), Barros (1929), Brauer (1930) among dealers in parrots and by Wagner (1886), McClintock, Badger (1929), Ellicott and Halliday (1931) and many others (see Meyer, 1934) among owners of pet shops and department stores, employees in Zoological Gardens (London and Washington) and finally seamen and baggage car employees connected with the transportation of birds, those associated with the shell parakeet trade in California have claimed absolute immunity against this malady. They argued that the alleged disease would have attacked primarily those who are intimately in contact with the infected birds and hence they must be immune. Some credence was given to these arguments until sputum examinations and more recently serum tests proved several so-called 'attacks of influenza with pneumonia' in bird breeders to be psittacosis. Today it is a fact that of 91 cases of psittacosis infections reported in California 36 or nearly 40 per cent were in owners of large or small parakeet aviaries or pigeon lofts or in members of their families. It is naturally a matter of conjecture but the few data thus far available from serological tests among raisers of birds would indicate that subclinical infections may in part explain the apparent immunity of some of the men and women who were exposed without any ill effects to heavily infected parakeets, parrots or pigeons. For example the caretaker in one of the infected aviaries gave a complement fixation reaction in a dilution of 1:16; the owner of a pigeon loft reacted in a like dilution and at least two of the five keepers of birds who were exposed to the same sources responsible for two clinical infections in a Zoological Garden had antibodies in their blood sera. Thus it appears that the supposed immunity in a group of bird breeders is either non-existent or only relative. One man developed his psittacosis about 3 weeks

other hand, it must always be remembered that susceptibility of man to the psittacosis or ornithosis virus is quite variable, and atypical pneumonias may in their ultimate analysis be attributed to the pigeon virus. In future, a negative history of exposure to psittacine birds should not exclude an inquiry into the possibility of contact with pigeons and chickens. The extent and the importance of such exposures must be ultimately judged by the experiences of the future.

Through the courtesy of Dr. Ruth E. Taylor of the Health Service, University of Chicago, an opportunity was afforded in 1939 to test the serum of a zoology student, who had clinical signs of a mild psittacosis. Her serum gave a specific reaction in a dilution of 1:16, and 7 of the 11 doves (*Streptopelia*) used by her for experiments reacted in a dilution of 1:8 and above. Since the organs had been preserved in glycerine, the attempted isolation of the virus was non-successful. This incomplete but, in its epidemiologic phases, conclusive observation formed the prelude to four other human cases with one fatality, which have been brought to the attention of the laboratory in 1940. Others doubtless have occurred, several positive sera from New York and Boston were collected from patients with probable exposure to barn yard birds, homing pigeons or doves. The extent of the pigeon infection may be merely surmised. It may be world-wide. At least, it has been definitely observed and proven by Coles in South Africa (Transvaal). A study of the host-parasite relationship and more than ever the ecology in the pigeon lofts must be studied in order to understand the infrequent clinical infections among pigeon fanciers and the personnel attached to breeding establishments. This will be a long and arduous task.

VIII THE ECOLOGY OF HUMAN PSITTACOSIS AND ORNITHOSIS INFECTIONS

The word "psittacosis" is primarily used to designate a peculiar contagious disease of man, which may follow either fleeting or prolonged exposure in a room, house, pet store or aviary where visibly diseased or apparently healthy parrots, parakeets, canaries and pigeons are held in captivity. Since late in 1929 and in no way connected with the pandemic era, a total of 273 cases of psittacosis with 47 or 17 per cent deaths have been clinically recognized in the United States and Canada. With the exception of 5 cases due to contact with Panama parrots, 5 to pigeons, 3 to canaries, 1 to love-birds, 1 to chickens and 4 to laboratory exposure, the infection chain in 252 cases either through laboratory tests or by mere induction incriminates locally bred and raised shell parakeets. It is indeed regrettable that at least 190 cases were directly traceable to budgerigars which originated from commercial aviaries in California. During the same period up to 1939 Fortner and Pfaffenberg, and Haagen and Mauer report from Germany on 353 cases and 69 or 18 per cent deaths nearly exclusively due to contact with parakeets raised in captivity. With the increased efficiency of the import regulations and the corresponding checking of the sources of infections through exotic birds, the control of psittacosis becomes a strictly domestic problem. Certain practices in the parakeet breeding and a trading industry have been largely responsible for these unfortunate and preventable

tion, it is well to remember that severe psittacosis is not uncommon in mid-summer

The greater frequency of psittacosis in *women* (for example in California 60 women 31 men or 2:1), in Germany 33:19 (Pfaffenberg) 17:8 (Haagen and Mauer, 1939), is in part due to the fact that they are either engaged in the breeding of parakeets for their livelihood, or that as lovers of pets they come more frequently in contact with the birds. Where the interest in the bird raising business has shifted to the male sex, their liability to infection is well documented by an increased incidence.

The pathways of transmission of the psittacotic virus from birds to man are probably twofold, and the order of importance is as follows: (1) Indirect transmission by the aerogenic route and aerial convection. (2) Direct contact through the handling of the corpse of a bird which had died, by feathers or excreta, by nasal discharge and through traumatic injury-like bite wounds. An apparent high contagiousness of a virus of high infectivity is fully attested in the histories in which very short exposures occurred in pet shops, households and baggage cars where diseased birds were kept. In fact, the dispersion of the virus particles adherent to the desiccated faecal droppings may be readily demonstrated in "sentinel experiments" as advocated by Meyer and Eddie. By exposing icebirds for varying lengths of time in rooms which house sick or latent infected parrots in a manner that excludes ingestion of feed contained with droppings, the experiences in human psittacosis epidemiology may be reproduced as perfect models. Furthermore, the ease with which inhalation of virus induces pneumonic lesions in susceptible mammals amply attests to the respiratory tract as the principal portal of entry for the virus. Finally, the main incidence of the infection in human cases falls on the respiratory tract, in cases of any severity, lobular distribution of the pneumonic consolidation and inflammation of the mucosa of the upper respiratory tract is a constant feature of those patients which come to autopsy. Under certain circumstances, the psittacotic virus prepares the way for the invasion of pathogenic bacteria which may, for example, cause a fulminating staphylococcic pneumonia.

The observations and reports attest with increasing frequency *human case to case infections*. At least 23 instances involving 30 nurses are known in which contact with the sick birds in the household are definitely excluded. Of particular interest is the fact that non-fatal cases may infect their nurses (Pittsburg outbreak) or that passage from man to man reduces the infectivity. Hamel reports a triple chain infection at Potsdam in which a physician, who contracted his disease from a fatal case, was visited by an interne. The latter developed psittacosis but recovered. During his illness he infected his nurse who died, and she in turn transmitted the virus to a second nurse. More recently, Haagen and Kruckeberg saw twice repeated human to human passage. A patient infected her nurse who in turn transmitted the virus to another patient temporarily housed in the same room. Even more disconcerting is the recent report by Pinero Garcia, who studied an outbreak of psittacosis in Buenos Aires in 1939. The epidemic involved 26 cases with 13 deaths. It started in a family, extended

after acquiring his bird stock, while 5 maintained aviaries with parakeets between 2 and 3 years before they became infected. The possibility that the aviaries were originally free from psittacosis, but were subsequently infected by purchase, exchange or barter of diseased shell parakeets cannot be excluded in every instance (Hoge). In pet shops the heavy exposure may lead to an attack rate of from 40 to 50 per cent.

Aside from these occupational psittacosis infections, the majority of reports deal with either single or more frequently multiple cases in the households of people who had bought or had received during the holidays the virus-carrying gift in the form of a pair of parakeets. People of middle age, rarely children, are involved. According to Armstrong, the age group of 1 to 19 was represented by 15 or 8.8 per cent in 169 cases. Of the 160 psittacosis infections of known age in Germany, only two were under 10 years of age, and 18 between 10 and 20. Intimate exposure of children to the same parakeets which infected parents or older relatives indirectly has been repeatedly noted. Aside from the low incidence, it is a common experience that children, as a rule, have much milder attacks of illness than the older patients in the family. Indeed, no explanation can be offered for the noteworthy fact that the same degree of contact and the same virus may induce diseases of varying degrees of severity. That the susceptibility of man is quite variable, and that a fair percentage may pass readily through the disease in a subclinical, rudimentary or abortive stage is fully attested by recent observations. The wife of a psittacosis patient exposed to a sick parrot, who picked seeds from a lip, passed through a very mild influenza-like illness of 2 days duration. Since her serum reactions were of the same magnitude as those of her husband, little doubt exists that the same virus led in the man to a severe clinical and in the wife to a subclinical infection. In isolated cases, the exposure to sick or healthy birds may induce clinical manifestations which in any one patient or in any stage of the malady are insufficiently characteristic to make a diagnosis. Particularly, in view of the increasingly important recognition that certain types of influenza or atypical pneumonias may be caused by psittacosis-like viruses, it is well not to be biased and to suspect this infective agent until laboratory tests, in particular the complement fixation tests and repeated sputum examinations, which unfortunately only furnish significant information in about one-half of the serologically proven cases, have decided the diagnosis one way or another.

The great epidemics of psittacosis of the past occurred during the winter months, and in Germany and Argentina the predominance of the disease during the colder months is striking. Observations in the United States have shown that the seasonal fluctuations were influenced by the prevalence of actively shedding birds, and by the prolonged exposure in the closed rooms of winter households enriched by a Christmas gift in form of birds. Attention has already been called to the effect of climatic changes on latent infected parakeets and parrots in the course of transportation from the aviaries to pet shops during the fall and winter months. Although the prevailing disposition to respiratory infection during the colder months of the year may favor the course of the infec-

fourth week after recovery from his psittacosis was due to an embolic accident, at least suggest such possibilities. Moreover, the circumstances surrounding the second attack of at least three persons originally proven cases of psittacosis strongly suggests relapses and not reinfections. Recent studies on the immunity in mice and birds strongly incriminate the phagocytic activity in part aided by humoral substances as the mechanism which restrains the virus growth (Meyer, 1941). Factors which induce the phagocytic activity may favor multiplication and spread of the virus and thus overwhelm the balanced immunity. It is not unlikely that the acquired immunity of man may be quite often of the non-sterile type, and since the equilibrium between parasite and host is quite fragile and labile, relapses may be anticipated and should receive consideration in future observations.

IX PROTECTIVE MEASURES AGAINST PSITTACOSIS OR ORNITHOSIS

Psittacosis has advanced to the position of an important public health problem which could be readily controlled provided the public would appreciate the possible danger inherent in contact with birds of unknown origin. The importations of tropical psittacine birds may be regulated by strictly enforced quarantine measures. But since it is not possible to say from the appearance of a bird whether or not it is infected and since parrots with inapparent infections may remain shedders of the virus for many months or, when subjected to crowding under insanitary conditions, may reactivate their latent infections prolonged isolation—not less than 6 months—is obviously imperative. This period of segregation may be shortened in the case of the larger parrots which may readily be bled from the wing veins: their sera may be subjected to the newly developed complement fixation for psittacosis. Birds which give positive reactions must be either destroyed or held until their sera become negative, while the non-reacting parrots must be retested within 2 months. If no antibodies develop in their sera they are non-infected and may be safely released. Experience has taught that, despite a properly executed health certificate, untested parrots may as avian carriers introduce the infection into healthy aviaries or dealers' stock.

The exclusion of psittacosis from shipments of parakeets, parrotlets and conures or the eradication of the endemic infections from the breeding establishments is likewise within the power of a Health Department although the administrative and laboratory procedures are slightly different. The California plan which has as its ultimate aim the complete eradication of the avian disease from the aviaries and the distribution and sale of healthy pets in the North American continent, has been tried for the past 6 years with increasing success. In principle, it has operated as follows. Any person or party who wishes to sell or barter parakeets must (a) obtain a license and receive a certificate of registration and (b) must submit a 10 to 20 per cent sample of his breeding stock and immature young birds to a laboratory examination. Aviaries yielding infected birds should be promptly placed in quarantine, the necessary steps taken to destroy the entire flock and to disinfect thoroughly the premises. The extent of the latent infections in the aviaries and the progress of the sanitation program

to house guests and terminated in the Jewish Hospital. At first, the nature of the influenza-like bronchopneumonia was not recognized and, consequently, secondary human to human contact infections followed. At the hospital one doctor, three nurses, two patients and one visitor contracted the infection directly through exposure to the unrecognized psittacosis patients. Furthermore, there is suggestive evidence that these secondary cases were responsible for tertiary infections. These aberrant chain transmissions are still regarded as epidemiological curiosities and rarities irrespective of the fact that they continue to occur, and that they may sometimes be an aid to the ultimate identification of the virus which may have operated in the hospital. The history of a small outbreak among three nurses with two fatalities, all connected with one patient in a San Francisco hospital supposedly due to a mysterious pneumonitis virus (Eaton and Pearson), has all the epidemiologic markings of a psittacosis infection. It is indeed imperative to remind every physician that the occupational hazard to himself and to the nurses is considerable. Every case of atypical pneumonia should be held in strictest isolation, and should not be examined or treated without the use of face masks and goggles. As occupational infections aside from nurses and physicians, those of sanitary inspectors and veterinarians must also be listed. At least, 45 serious laboratory infections have been reported. Despite the introduction of precautionary measures in various forms, these professional infections have made their appearance even in recent years.

The incubation time varies from 7 to 14 days after initial exposure. From 2 to 3 weeks may elapse between the acquisition of the birds and the onset of the first case. In three cases in which a single exposure occurred for a few hours, the incubation time was 7, 8 and 9 days, respectively. The interval between onset of the illness and the discharge of the nurse from the case was 8, 13 and 30 days, respectively. From personal observations and the many clinical descriptions published since 1879, it is evident that the manifestations repeat themselves with remarkable regularity and uniformity. It is this pattern of signs and symptoms aided by x-ray pictures of the chest which enables the experienced physician to suspect psittacosis.

The case fatality rate of the reported cases has been remarkably uniform both in the United States and in Germany. In the 167 cases reported by Armstrong, it was 24 per cent, for the 271 cases since 1931 it is 17 per cent, and for the 91 cases in California it is 22 per cent. According to Fortner and Pfaffenberg, the rate was 18 per cent in 1933-1934 for 106 cases, then 20 per cent but rose to 36 per cent in group of 25 cases in 1937-1938 (Haagen and Mauer). As a rule, the age groups 40 to 60 are particularly liable to fatal infections.

An infection, which in the avian and mammalian host is so frequently latent, in all probability induces a similar state in man. Whether "silent carriers," supposedly demonstrated by Geilach in certain hospital patients, really exist requires further study. The persistence of complement fixing antibodies at a high titer for years in the sera of recovered patients, and the isolation of the virus by Haagen and Kruckeberg from the spleen of a patient whose death during the

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is well illustrated by the data in Table 3, which covers the postmortem examination of approximately 26,000 parakeets

Experience has taught that aviaries which harbor infected budgerigars may have a very low mortality from actual psittacosis. This is particularly true when the sexes are held in separate pens and breeding operations have ceased. But with the resumption of these activities, psittacosis reappears in a few of the immature birds. Thus, the contagium tenaciously persists for years, and in time as many as 40 to 80 per cent of the young parakeets may show the residuals of latent infections. Recent observations indicate that one test based on a 20 per cent sample will not always detect the existence of psittacosis in an aviary. However, annual retests and a more rigid supervision of dishonest breeders, who may unknown to the control authority introduce parakeets from private untested aviaries, should in time eradicate the infected stock in California. This is the goal towards which the California State Department of Public Health is striving. Provided adequate funds are available for the laboratory tests, no unsurmountable difficulties are anticipated. An effective educational campaign has greatly softened the opposition of the breeders and dealers, who at first failed to admit that such a disease as psittacosis really existed or that it might be transferable to man.

The extent of Ornithosis in pigeons and the risk of this infection to human beings is not as yet known. At least for the present, it is well to focus the control measures on the psittacine birds, while the problems which involve the barnyard and pigeon lofts are being subjected to a careful analysis.

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THE NATURAL HISTORY OF LAENNEC'S CIRRHOSIS OF THE LIVER

AN ANALYSIS OF 386 CASES

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The etiology of Laennec's cirrhosis is unknown. In an attempt to understand this disease, it is essential to ascertain the nature of those factors that predispose or contribute to its incidence. It is also important to know its symptomatology and course in order to evaluate the effect of therapeutic measures. The older medical literature contains few reliable studies in these respects. The addition of certain diagnostic measures in recent years may account for more accurate differentiation between cirrhosis of the liver and other diseases, such as tuberculous peritonitis, Pick's disease, cardiac cirrhosis, and other affections. The comprehensive reports of Rolleston and McNee (227) and Eppinger (73) did much to clarify the clinical picture of Laennec's cirrhosis. The present survey is an attempt to establish further certain facts pertinent to the natural history of the disease.

There have been differences of opinion concerning the definition of Laennec's (portal) cirrhosis as seen on pathologic examination. However, in this analysis no distinction has been made between the terms portal cirrhosis (whether atrophic or hypertrophic) or Laennec's cirrhosis of the liver. In the present series are included four patients who had a history of exposure to inorganic arsenic or other toxic agents and who may represent instances of healed yellow atrophy (toxic cirrhosis). In the literature, nodular cirrhosis, multilobular cirrhosis, chronic (interstitial) hepatitis, nodular cirrhosis and gin-drinker's liver are frequently used to describe the pathologic lesions of portal cirrhosis, though the same terms are sometimes used to define other lesions of the liver as well.

CASE MATERIAL

Eight hundred sixty-five charts on which the diagnosis of "cirrhosis of the liver" appeared were reviewed from the files of the Babies, Beth Israel, New York, Mount Sinai and Presbyterian Hospitals, all of New York City.¹ Three hundred eighty-six cases were considered to show adequate clinical evidence of cirrhosis. Of these, 178 were established by histologic examination of surgical or post-mortem specimens, whereas 208 were classified as "presumptive" cases. The latter were patients whose history and physical examination bore presumptive evidence of the disease. Such evidence included the finding of palpable liver and spleen, signs of collateral venous circulation, jaundice, ascites, roentgenologic signs of esophageal varices, hematemesis, and laboratory tests revealing abnormal liver function. Several of these abnormalities were gen-

¹ The authors wish to express their thanks to the medical and record room staffs of the above hospitals for making available the charts analyzed in this study.

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nec's cirrhosis The large number of Jewish patients is seen to be the result of a sampling error since two large Jewish hospitals were included in this study The number of Italian and Irish patients with cirrhosis of the liver appear to exceed the proportion of these races in the consecutive hospital admissions

There are few other reports concerning the race incidence of cirrhosis in the United States Richardson (218) found in Boston that 42 per cent of 48 patients with Laennec's cirrhosis were Italian as compared with 13 per cent incidence of Italians in the general hospital population

Since cirrhosis of the liver is not a reportable disease it is impossible to obtain adequate data regarding its clinical incidence Difficulties in establishing the diagnosis of the disease likewise render such data unreliable For this

TABLE 2
Race and sex distribution of 585 cases of Laennec's cirrhosis

RACE	FRESHWATER		N. Y. HOSP.		S. I. HOSP.		BASINS HOSP.		MT. S. HOSP.		TOTAL		PER-CENT-AGE OF CASES	PER-CENT-AGE OF CONTROL
	M	F	M	F	M	F	M	F	M	F	M	F		
U. S. *	25	10	27	11	2	2		1	4	1	58	25	21.4	24.0
Jewish	5	3	6	2	19	10			23	12	53	27	20.7	30.7
Italian	18	1	27	6		1	2	1	8	1	55	10	16.9	8.5
Irish	14	9	16	13	1		1		3	2	35	24	15.3	8.2
German	10	3	3	3							13	6	4.9	4.8
English	6	3	2	2							8	5	3.4	2.5
Negro	7	5							1		8	5	3.4	1.6
Greek	3		4						1	1	8	1	2.3	1.1
Czech	2	1	3	1							5	2	1.8	1.3
Austrian	1		2	1						1	3	2	1.3	2.6
Puerto Rican			1						3	1	4	1	1.3	1.9

Also 4 each—Polish, 3 each—Scotch, Swedish, Canadian and Hungarian 2 each—Spanish Armenian, and Chinese 1 each—Cuban Barbados White, Russian, Turkish Finnish and Swiss

* U. S. includes all patients whose race was not recorded

† Calculated from 1600 control patients, and weighted in proportion to the total number of admissions to each hospital

reason a comparison of mortality data should provide a better index to the frequency of cirrhosis in different regions Rowntree (229) reviewed the incidence of cirrhosis in a number of foreign countries He found that the death rate from cirrhosis for each 100,000 of the population was highest in Italy and lowest in Norway Table 3 is a compilation of selected data on the incidence of cirrhosis throughout the world The wide variation not only from country to country, but within the same country, is immediately apparent A similar variation was noted by Rabl (207) and by de Josselin de Jong (69) who made extensive surveys of the geographic incidence of cirrhosis

In the present series there are few patients from the Near East and Orient, where cirrhosis is relatively frequent In these regions the high incidence of cirrhosis of the liver has been attributed to environmental factors, such as

erally present before the diagnosis was considered to be certain. Care was taken to exclude those cases in which it was not clear whether hematemesis, for example, was due to bleeding peptic ulcer or to ruptured esophageal varix.

The 479 cases which were excluded from this study fell roughly into 3 groups:

(1) Cases in which the evidence for cirrhosis was absent or equivocal, or in which there was a definite suspicion that the symptomatology was referable to other causes. There were 351 such cases. Of these there were 67 in which a palpable liver was the only sign which led to the diagnosis of cirrhosis.

(2) Cases which proved on histologic examination not to be Laennec's cirrhosis, or which were complicated by primary carcinoma of the liver. There were 79 cases in this group, of which 24 were cirrhosis of the liver with primary carcinoma, and 6 were hemochromatosis.

(3) Cases in which Laennec's cirrhosis was discovered at post-mortem as an incidental finding. As far as could be ascertained from the records, these

TABLE 1

Distribution of 386 cases of Laennec's cirrhosis according to hospital admissions

HOSPITAL	YEARS	TOTAL ADMISSIONS	CASES OF LAENNEC'S CIRRHOSIS		
			Proved	Presumptive	Total
Babies	1929-1938	25,500	5	1	6
Beth Israel	1924-1938	86,500	14	22	36
Mount Sinai	1933-1937	72,000	33	34	67
New York	1923-1938	163,500	53	86	139
Presbyterian	1916-1937	214,500	73	65	138
Total			178	208	386

cases were asymptomatic. There were 49 cases in this group, or 11 per cent of the total clinical and latent cases.

The distribution among the several hospitals of the cases included in this series is listed in table 1.

ANTECEDENT FACTORS

Race and nationality

The polyglot population of New York City lends itself to the study of the racial incidence of disease. A true estimate of race incidence, however, requires a knowledge of racial distribution of the population in each hospital studied, as well as allowance for age distribution of these groups. Such data are not available. In lieu of this, only a rough approximation could be made of any racial preponderance of this disease. Comparison was made of the proportion of patients of each race with a sample of consecutive admissions to the several hospitals. Native-born patients of foreign-born parents were considered arbitrarily to belong to the stock of the mother.

Table 2 lists the number of patients of each race or nationality with Laen-

malaria, dysentery, and possibly nutritional deficiency (313, 260, 168, 212) The predilection of cirrhosis in this country for persons of Italian and Irish descent may also be due to environmental factors such as alcoholism and nutritional deficiency It is of interest that in a recent survey of pellagra in California (244), the incidence among Italians was especially high, when allowance was made for the proportion of Italians in the population Since cirrhosis of the liver occurs in all races, it seems more likely that environmental rather than constitutional factors determine the differences in race incidence

Hereditary and constitutional factors

There are numerous case reports of cirrhosis of the liver occurring in families For the most part, these have been in children (35, 227, 264, 145, 175) In most instances, no known exposure to toxic agents has been discovered In the present series of 386 cases there was one instance in which a sister and brother, aged 11 and 12 years, both had cirrhosis

Among the adult patients, none gave the history of a familial incidence of the disease This negative finding apparently is in accord with other large series (227, 74, 207) in which no mention is made of a familial incidence of Laennec's cirrhosis in the adult In occasional cases where cirrhosis has been reported to occur in families, it seems likely that the onset of the disease was determined by environmental rather than hereditary factors (132, 72) This interpretation is supported by the experience of the authors, who treated one of two sisters with Laennec's cirrhosis (confirmed by autopsy) Both sisters were chronic alcoholics

Chrostek (61) and others have described constitutional characteristics of patients with Laennec's cirrhosis The typical patient with Laennec's cirrhosis was said to have a long torso and either a female distribution of body hair or a relative lack of body hair Since the case histories in the present series do not take account of these factors, it is not possible to affirm or deny the predisposition to the disease by persons with certain constitutional make-ups In a carefully studied series of 54 patients (192) we have observed no characteristic diathesis Since the disease occurs in all races, and since it shows little tendency to occur in families, the constitutional factor seems unimpressive

Nevertheless, there are two forms of cirrhosis of the liver which appear to be congenital and which resemble Laennec's cirrhosis histologically The first of these is Wilson's disease (304) which is characterized further by bilateral symmetrical degeneration of the lenticular nuclei The cirrhosis in Wilson's disease is usually asymptomatic (12) The second is hereditary angiomatosis, which in several well-described cases has preceded the development of Laennec's cirrhosis in several members of a family (279, 289) In view of these conditions it is possible that constitutional factors play a role in the etiology of Laennec's cirrhosis, even though the outward manifestation of body build and hair distribution show no peculiar pattern in these patients

TABLE 3

The incidence of Laennec's cirrhosis in autopsy material

COUNTRY	REFERENCE	YEAR	PER CENT ALL CIRRHOSES	PER CENT LAENNEC'S CIRRHOSES
United States				
Los Angeles, California	75	1918-1932	0.65	
Los Angeles, California	75	1933-1937	1.86	
San Francisco, California	106		5.0	
Baltimore, Maryland	189			6.3
Baltimore, Maryland	111	1890-1929	2.2	
Boston, Massachusetts	43	1912	1.04	
Boston, Massachusetts	158	1897-1932	5.89	2.9
Minneapolis, Minnesota	165	1910-1931		2.05
St. Louis, Missouri	190	1921	1.6	
New York, New York	263	1917		1.72
Cincinnati, Ohio	241	1938	4.7	
Portland, Oregon	169	1933	1.37	0.43
Philadelphia, Pennsylvania	29	1933-1935	6.1	3.75
Philadelphia, Pennsylvania	28	1938-1939	5.3	1.0
Canada				
Montreal	3	1886-1898	4.9	
Ceylon	278	1934-1935	5.6	
China	73		12.0*	
	311	1928	4.4	
England				
London	37	1867-1899	3.52	
London	46	1901-1906	7.7	
Manchester	137	1897	4.0	
Germany				
Breslau	153	1878-1907	2.67	
Leipzig	207		1.8	
Senckenberg	26	1920	1.55	
Holland				
Amsterdam	109	1921-1929	2.0	
Utrecht	69	1931	2.85	
India				
Calcutta	223	1911	6.9	2.82
Vezagapatnam (South India)	273	1925-1934	9.3	5.2
Madras (South India)	168	1927-1931	4.4	
Italy	40		1.73	
Japan	136	1924	1.77	
Netherlands East Indies	31	1931		2.6
Philippine Islands	13	1907-1930		0.99
Sweden	116	1931	4.4	2.85
Switzerland				
Geneva	7	1931	9.4	6.95
Zurich	171	1930-1931	10.1	4.5
Turkey	268	1931	4.4	3.63
U S S R				
Leningrad	207		1.1	
Moscow	207		0.9	
Kiev	207		1.4	
Baku	207		4.4	
Tiflis	207		3.7	

* Including 5 per cent schistosomiasis

of the liver reported in the modern American and European literature is approximately the same as that of the patients in this series (159, 74)

Most authors have found that the disease occurs slightly earlier, on the average, in women than in men. Henrikson (115) found that the average age of 124 males with cirrhosis was 50 years and of 38 females, 45 years and Rolleston and Fenton (226) found that among patients dying of cirrhosis, the average age of males was 50 years, and of females 46 years. This is an interesting parallel to the incidence of alcoholism. In a survey of 18 000 admissions for alcoholism to Bellevue Hospital, New York City (144), it was noted that the age group of highest incidence for males was from 33 to 37 years, and for females, from 28 to 32 years. The age group of peak incidence for males who

TABLE 4
Age distribution of patients with Laennec's cirrhosis at time of onset

AGE	MALE	FEMALE	TOTAL
<i>AGES</i>			
0-4	2	1	3
5-9	2	1	3
10-14	1	4	5
15-19	1	2	3
20-24	1	2	3
25-29	7	4	11
30-34	9	7	16
35-39	21	12	33
40-44	29	25	54
45-49	55	16	71
50-54	49	21	70
55-59	47	14	61
60-64	29	7	36
65-69	10	2	12
70-74	2	1	3
75-79	2		2
Total	267	119	386

were certified to have died from alcoholism in the United States from 1934 to 1938 was from 50 to 54 years, while the peak for females was between 35 and 39 years (234)

In countries where the life expectancy is short, the peak of greatest incidence of cirrhosis falls earlier than in the United States or Europe. Thus in Calcutta (223), 59 per cent of 213 patients who had cirrhosis at autopsy were between 21 and 40 years of age, and in Madras, in Southern India, 65 per cent of 177 patients with portal cirrhosis were between 30 and 49 years (168)

Statistics dealing with the incidence of cirrhosis in children are in general unsatisfactory since differentiation between congenital syphilis of the liver, obstructive cirrhosis due to congenital abnormalities of the biliary tract, and true portal cirrhosis is usually not made. Of 9,000 autopsies on children less

Sex incidence

Laennec's cirrhosis occurs in males more than twice as frequently as in females. There were 267 males and 119 females in this series. Although the ratio of males to females among the several nationalities is approximately 3 to 2, or 2 to 1 (cf. Table 2), there are more than 5 males for each female among the Italians, and of 9 Greek patients only one is a female. It is to be noted that of the 11 Italian and Greek women in this series, only 2 gave a history of alcoholism, and none had syphilis.

Rolleston and McNee (227) collected 645 cases in the British literature and found that of these 74 per cent were in males. Of Eppinger's 373 cases (73), 72 per cent were in males. McCartney (165), studying autopsy material, noted that although 70 per cent of patients who had symptoms of cirrhosis during life were males, 87 per cent of the latent cases were of that sex. De Josselin de Jong (69) reviewed the sex incidence of hepatic cirrhosis throughout the world. He observed that there was wide variation not only from country to country but within the same country. On the average, cirrhosis was from two to three and a half times more frequent in men than in women. Unfortunately, his series included no data from Italy or Greece.

✓ The predilection of cirrhosis for males has long been attributed to their higher incidence of alcoholism (39, 144, 131, 27, 228). Of the 16,692 persons certified to have died of alcoholism in the United States between 1934 and 1938, 87.9 per cent were males, and 12.1 per cent females (234). The role alcoholism plays in determining the high percentage of male patients with cirrhosis is corroborated by the fact that in 58 instances of non-alcoholic Laennec's cirrhosis in children, gathered from the literature, equal numbers of cases occurred in each sex.

It can be concluded that Laennec's cirrhosis of the liver is a disease which occurs at least twice as frequently in males as in females, a fact which is probably explained by the higher incidence of alcoholism in the former sex.

Age distribution

Although characteristically a disease of late middle life, Laennec's cirrhosis may occur at any age. In 84 per cent of this series, the first symptoms appeared between the ages of 35 and 64 years, and in 66 per cent, between 40 and 59 years. The youngest patient was a two year-old girl, and the oldest was a 76 year-old carpenter. Table 4 lists by 5-year periods the number of patients in each group. It may be noted that the peak incidence for females occurs five years earlier than for males.

Since the number of persons in the population falls off sharply in the late age groups, it is essential to make a correction for the age distribution of the general population. Figure 1 represents the ratio of the percentage of patients with cirrhosis in each age group, divided by the percentage of the population of New York City in the same age group, according to the 1930 United States Census. The corrected age morbidity incidence for all cases is seen to reach its peak between the ages of 55 and 59 years. The age of patients with cirrhosis

hospitals For lack of other norms, these served as approximate control data The occupations of the patients in this series are listed in Table 5 By comparison with the controls it is apparent that liquor and food handlers are somewhat prone to develop cirrhosis Laborers also have a high incidence of the disease The remaining data are not definitive

The frequent occurrence of cirrhosis among those who handle alcoholic liquors professionally was described early (77, 74, 221, 81) In various series

TABLE 5
Occupation of 583 patients with Laennec's cirrhosis

OCCUPATION	NUMBER OF PATIENTS	PER CENT OF PATIENTS	PER CENT OF CONTROL SERIES*
Housewife	79	20 $\frac{1}{2}$	31 $\frac{1}{2}$
Laborers and porters	24	6 $\frac{2}{3}$	3 $\frac{2}{3}$
Bartender, liquor dealer, brewery worker	19	4 $\frac{9}{10}$	0 $\frac{1}{10}$
Cook, baker, caterer, restaurateur	18	4 $\frac{7}{10}$	2 $\frac{0}{10}$
Clerk, stenographer, secretary, etc	17	4 $\frac{4}{10}$	6 $\frac{7}{10}$
Salesman, saleslady	14	3 $\frac{6}{10}$	2 $\frac{7}{10}$
Chauffeur, truckman	13	3 $\frac{4}{10}$	1 $\frac{3}{10}$
Mechanic machinist, electrician	11	2 $\frac{9}{10}$	1 $\frac{5}{10}$
School	9	2 $\frac{3}{10}$	11 $\frac{3}{10}$
Painters	8	2 $\frac{1}{10}$	0 $\frac{8}{10}$
Time keeper watchman	8	2 $\frac{1}{10}$	0 $\frac{6}{10}$
Cabinet maker, carpenter	8	2 $\frac{1}{10}$	1 $\frac{0}{10}$
Waiter, dishwasher, counterman	8	2 $\frac{1}{10}$	1 $\frac{3}{10}$
Domestic	8	2 $\frac{1}{10}$	2 $\frac{7}{10}$
Shoemaker, bootblack	7	1 $\frac{8}{10}$	0 $\frac{2}{10}$
Factory worker	7	1 $\frac{8}{10}$	2 $\frac{4}{10}$

Also 6 each—sailor, sailor-peddler, $\frac{1}{2}$ each—barber, policeman, laundry worker, artist foreman storekeeper, printer, 3 each—iceman physician contractor teacher, engineer, hatter, cigar maker 2 each—stationer, entertainer, minister, seaman, railroadman milliner butcher, executive elevator operator junkman, chemical worker 1 each—press-puncher, boardinghouse keeper, steam-fitter, boiler-maker, iron-worker scrap-iron worker, confectioner investigator companion, stableman, gardener, plumber merchant furniture-polisher jeweler gargaman lawyer, interior decorator doll-maker paper-hanger, hat-cleanser broker coal-miner, usher, wife of restaurateur, wife of bar-tender, toxicologist, sign gilder boxer sports instructor, stationary fireman

No occupation 19 duplications 12

* Control group of 1200 consecutive admissions divided among the various hospitals

from India (212, 110) and the Orient (287, 261) cirrhosis seems to be common in farmers Rowntree (229) points out that in the United States both alcoholism and cirrhosis are less prevalent in rural than urban areas This is also said to be true in England and German (278a)

Laennec's cirrhosis is thus a disease which is prone to occur in those occupational groups in which there is ready access to alcoholic beverages In addition, there are isolated cases which are the result of occupational exposure to other toxic agents

than 12 years old in England, there were 20 cases of cirrhosis "similar to chronic interstitial hepatitis met with in spirit-drinking adults", of these, 2 might have been due to syphilis (254) Of 246 autopsies on children under 15 years of age at the Johns Hopkins Hospital, 4 revealed atrophic cirrhosis (111) The frequency of portal cirrhosis among pediatric hospital admissions is much lower, occurring, for example, once in 20,000 hospital cases (178)

$$\text{RATIO} = \frac{\% \text{ OF CASES}}{\% \text{ OF POPULATION}} \\ \text{1930 CENSUS NYC}$$

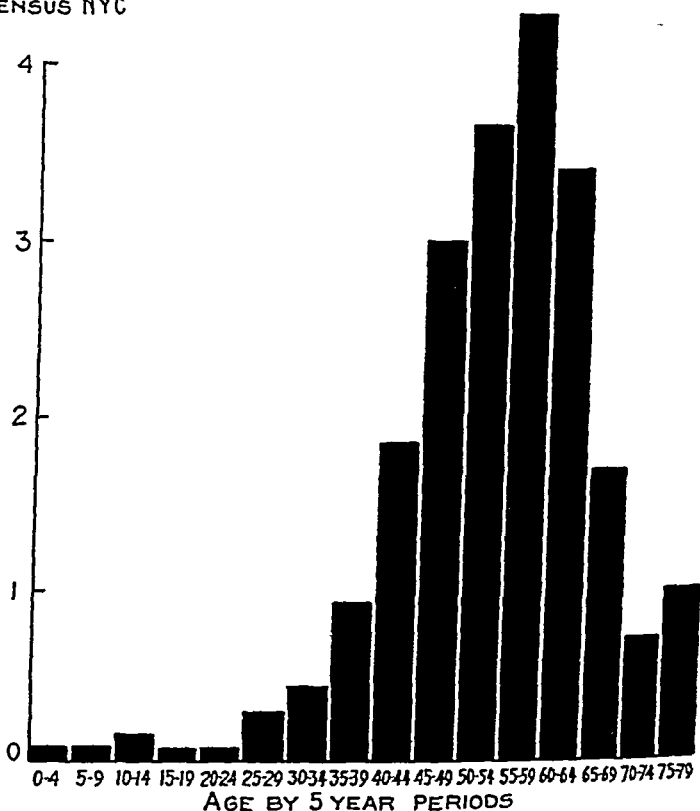


FIG 1 AGE INCIDENCE OF 386 PATIENTS WITH LAENNEC'S CIRRHOSIS

The chart is corrected according to the population of New York City in the same age groups, as derived from the 1930 U S census,

Laennec's cirrhosis is thus a disease particularly prone to occur between the fourth and seventh decades. It occurs earlier, on the average, in females than in males, this parallels the earlier incidence of alcoholism in the former sex

Occupation of patients with cirrhosis

The incidence of cirrhosis among the various occupational groups was analysed. Comparison was made with a group of 1200 admissions to the several

of beverage was unspecified Mills (174) in Montreal reported similar findings in 83 alcoholic patients with cirrhosis

Corroborative evidence concerning the importance of alcoholism as a forerunner of cirrhosis can be obtained from a study of the relationship between the incidence of each During the early years of Prohibition in the United States there was a prompt decline in the mortality rate of cirrhosis of the liver from the pre-prohibition level of 13 to 14 per 100,000 of the population, to about 7 per 100,000 (229) There was a parallel decline in the incidence of deaths from alcoholism Even more striking are the statistics on deaths from

TABLE 6
Incidence of alcoholism in patients with Laennec's cirrhosis

COUNTRY	REFERENCE	LATERAL	PER CENT ALCOHOLICS	PER CENT TOTAL ABSTAINERS
United States				
San Francisco	24	Clinical	86	
Los Angeles	75	P.M.	46	
Chicago	209	Clinical	78	
New York	183	P.M.	7½	
Philadelphia 1933-5	29	P.M.	30	
Philadelphia 1938-9	28	P.M.	45	
Canada	174	Clinical	77	8
England	226 312	P.M. P.M.	56 46	
Austria	74 74	Clinical Clinical	52 (male) 19 (female)	14 (male) 58 (female)
Switzerland	221 7	P.M. P.M.	56 39	
Philippines	13	P.M.	20	
China	257	Clinical	31	
Syria	313	Clinical	9	
India	212	Clinical	3	77
India	260	Clinical		84
Turkey	268	P.M.	2 5	

Key P.M. = autopsy statistics, clinical = per cent of patients with cirrhosis regardless of whether autopsies were performed

alcoholism and from cirrhosis in England during the first World War In 1914 there were 676 deaths from alcoholism, and 4,148 from cirrhosis, in 1918, 81 deaths from alcoholism and 1,730 from cirrhosis (256) Similar findings were noted in Germany and Russia (207, 235 21) Since the repeal of Prohibition in the United States there has been a rise in the death rate from cirrhosis, in 1937 the death rate was 8 5 per 100,000 of the population, the highest since 1918 (234)

Although none of the pediatric patients in the present series had a history of alcoholism there are frequent reports in the literature of cirrhosis in juvenile imbibers In 1887, R Palmer Howard (119) noted that of 63 cases of juvenile cirrhosis in the literature, 10 were in children with a history of alcoholism His

Rôle of alcoholism in the etiology of Laennec's cirrhosis

Two hundred seven patients, or 54 per cent of this series, gave a history of the habitual consumption of alcoholic liquors. Alcoholism was defined as the regular, daily consumption of at least one quart of wine, six glasses of beer, or four "whiskeys" (approximately 6 ounces). This consumption agrees roughly with the minimum defined by other observers, namely Barker (10), Bazzano (19), and Eppinger (74). This definition, admittedly, is arbitrary. It is based on the common observation that when this amount is estimated by the patient, his family or acquaintances often reveal that he understates the facts. In general, the intake of liquor by "alcoholics" far exceeded this minimum. Sixty per cent of the male patients, in contrast to 37 per cent of the female patients, admitted alcoholism. Probably the true incidence of alcoholism is higher. There is no evidence from this survey that one kind of alcoholic beverage was a more effective precursor of the disease than another.

The correlation between alcoholism and cirrhosis has long been noted. Vesalius (240) in the sixteenth century described "atrophy of the liver" in alcoholics, and Fernel (240) wrote that wine caused "scirrhus of the liver." In 1633 James Hart wrote, in a treatise entitled "Diet of the Diseased," that "strong waters produce an irrevocable scirrhus in the liver" (195). Although Richard Bright (1827) is generally credited with having called attention to the importance of alcoholism as a precursor of cirrhosis, the relationship must certainly have been well known before that, for in 1820 James Johnson (129) wrote, "In this country (England), among the internal exciting causes of hepatic inflammation, the ingurgitation of inebriating liquors and particularly ardent spirits has always been ranked foremost, yet I am convinced that the acute species of the disease is seldom induced in this way, though chronic derangements, especially of function, are in a great measure occasioned by those injurious potations."

The incidence of alcoholism in patients with cirrhosis in various countries is listed in Table 6. It can be seen that the frequency of alcoholism among patients with cirrhosis reported in this series is of the same order as in other American and European series. In Syria and India, however, only a small percentage of the patients admitted alcoholism, yet the incidence of cirrhosis in these countries is not lower than where alcoholism is commonly associated with the disease. Thus in Vezagapatam, South India, portal cirrhosis is present in 52 per cent of all autopsies (273), but only 3 per cent of patients with portal cirrhosis were alcoholics (260).

Although there are proponents for each variety of alcoholic beverage as the most potent precursor of cirrhosis, there is no good evidence that the form in which the alcohol is taken has any bearing on the frequency of the disease. Many writers have emphatically stated that those who drink strong liquors are more likely to succumb to cirrhosis than those who drink wines or beer (39, 163, 179, 144). Yeld (312) found that of 60 English patients with cirrhosis who admitted alcoholism, 11 were primarily beer drinkers, 19 drank "spirits," 11 used both indiscriminately, and there were 19 patients for whom the type

of beverage was unspecified Mills (174) in Montreal reported similar findings in 83 alcoholic patients with cirrhosis

Corroborative evidence concerning the importance of alcoholism as a forerunner of cirrhosis can be obtained from a study of the relationship between the incidence of each During the early years of Prohibition in the United States there was a prompt decline in the mortality rate of cirrhosis of the liver from the pre-prohibition level of 13 to 14 per 100,000 of the population, to about 7 per 100,000 (229) There was a parallel decline in the incidence of deaths from alcoholism Even more striking are the statistics on deaths from

TABLE 6

Incidence of alcoholism in patients with Laennec's cirrhosis

COUNTRY	REFERENCE	MATERIAL	PER CENT ALCOHOLICS	PER CENT TOTAL ABSTAINERS
United States				
San Francisco	24	Clinical	86	
Los Angeles	75	P.M.	46	
Chicago	209	Clinical	78	
New York	183	P.M.	74	
Philadelphia 1933-5	29	P.M.	30	
Philadelphia 1938-9	28	P.M.	45	
Canada	174	Clinical	77	S
	226	P.M.	56	
England	312	P.M.	46	
	74	Clinical	52 (male)	14 (male)
Austria	74	Clinical	19 (female)	58 (female)
	221	P.M.	56	
Switzerland	7	P.M.	39	
Philippines	13	P.M.	20	
China	257	Clinical	31	
Syria	313	Clinical	9	
India	212	Clinical	3	77
India	260	Clinical		84
Turkey	268	P.M.	2 5	

Key P.M. = autopsy statistics clinical = per cent of patients with cirrhosis regardless of whether autopsies were performed

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series included a number of cases which probably were not portal cirrhosis, but rather congenital syphilis of the liver, or congenital atresia of the bile ducts Jones (135), in 1907, made an excellent review of the literature up to that time, gathering 74 cases, including 2 of his own, of juvenile cirrhosis in which there was a history of alcoholism The symptoms in these juvenile cases differed "but little from those in the adult" The children in Jones' series were usually given the alcoholic beverages by their parents He pointed out that the dose of alcohol apparently effective in "causing" cirrhosis in children is proportionally smaller than in the adult

The sex incidence of alcoholism as it affects the incidence of cirrhosis has already been discussed

Although the frequency of alcoholism is high in patients with cirrhosis of the liver, the reverse correlation is not as good The incidence of cirrhosis among chronic alcoholics is variously estimated at from 1 to 30 per cent These data are illustrated in Table 7 A possible inference from the data is that al-

TABLE 7
Incidence of Laennec's cirrhosis in alcoholism

COUNTRY	REFERENCE	MATERIAL	PER CENT CIRRHOSIS
United States	85	P M	2.4
United States	29	P M	25.4
United States	163		4-6
France	27	Clinical	30.4
Germany	18	P M	5-6
Germany	73	P M	3.6
Germany	87	P M	1.0

coholism itself is not the sole cause of Laennec's cirrhosis of the liver The fact that the disease occurs commonly in India, Java, and Ceylon, where alcoholism is rare, supports this interpretation

Thus, the rôle of alcoholism in the etiology of cirrhosis is obscure In a review of experimental cirrhosis of the liver in laboratory animals, Moon (176) cited many unsuccessful attempts to produce the disease by the administration of alcohol Noteworthy are the experiments of Friedenwald (91) who was unable to produce cirrhosis in rabbits by the daily administration for 4 years of 5 to 8 cc of absolute alcohol diluted in 20 to 30 cc of water In a preliminary report (191) on the treatment of 13 patients with cirrhosis of the liver, and in a more detailed report (192) on 54 patients it was suggested that the correlation between alcoholism and cirrhosis of the liver might be due to co-existing nutritional deficiency, in a manner analagous to alcoholic beri-beri and alcoholic pellagra Such an hypothesis could explain the occurrence of cirrhosis of the liver in both alcoholic and non-alcoholic subjects

At the present time one may conclude that alcoholism is a common precursor of Laennec's cirrhosis of the liver, but that it is neither the only, nor necessarily the most important predisposing cause

Syphilis as a precursor of Laennec's cirrhosis

Syphilis was present in 62 patients, or 16 per cent of the patients in this series. This was recognized by either a positive serology or by the story of primary lesion and treatment. Sera showing only one or two plus reactions to the cholesterinized antigen and sera showing anti-complementary Wassermann reactions were considered to be negative. As far as could be ascertained, none of the patients in this series had syphilis of the liver. Thirty-four of the 62 patients previously had received arsenical therapy.

This high incidence of syphilis among patients with cirrhosis was recognized early, Frerichs (90) in 1860 reporting that 6 of 36 patients with cirrhosis had syphilis. In 1902, Sears and Lord (238) noted that among 78 patients found to have cirrhosis at autopsy, excluding any with active syphilitic lesions 12 per cent gave a previous history of syphilis. In this series, as well as in most others, a comparison with the incidence of syphilis in general autopsy material was not made.

Following the discovery of the Wassermann reaction, a number of authors reported that the incidence of syphilis among patients with cirrhosis was much higher than had previously been suspected (148, 262, 149). Perhaps because of improvements in the technique of serologic examination, recent series no longer include such high percentages of patients with syphilis. Boles and Clark (29), in 1936 reported the history of syphilis in 9.3 per cent of patients with portal cirrhosis at necropsy, and Evans and Gray (75), in 1938, noted that 12 per cent of 217 patients who had cirrhosis at autopsy were syphilitic.

Syphilis is found as a precursor of cirrhosis in countries where alcoholism is unimportant as a predisposing factor. Thus in Syria, 12 per cent of 70 patients had syphilis (313) and in Southern India (212) the sera of 41 of 55 patients with portal cirrhosis and ascites gave a positive Wassermann reaction. The high incidence of syphilis among patients with cirrhosis is without obvious explanation. Schumacher (237), who reviewed the literature on syphilis and cirrhosis and who reported 45 cases of cirrhosis from the New York Hospital, believed that 'syphilis long continued in association with alcoholism, and perhaps alone, may cause diffuse cirrhosis of the liver'. Ferris (79), however, has shown that in rabbits infection with *spirochaeta pallida* produced no significant increase in the incidence of cirrhosis induced by the injection of chloroform.

The concurrence of syphilis and Laennec's cirrhosis of the liver raises several questions. (1) What is the incidence of syphilis in comparable series of cases, whether clinical or autopsy material? (2) What is the incidence of cirrhosis in persons with syphilis? (3) What is the incidence of syphilis in chronic alcoholics without cirrhosis? (4) How valid is the Wassermann reaction in the presence of cirrhosis of the liver?

These control data are not at hand, and without them the significance of the association of the two diseases is questionable. One may conclude that syphilis is a rather frequent concomitant of Laennec's cirrhosis, the significance of

series included a number of cases which probably were not portal cirrhosis, but rather congenital syphilis of the liver, or congenital atresia of the bile-ducts Jones (135), in 1907, made an excellent review of the literature up to that time, gathering 74 cases, including 2 of his own, of juvenile cirrhosis in which there was a history of alcoholism The symptoms in these juvenile cases differed "but little from those in the adult" The children in Jones' series were usually given the alcoholic beverages by their parents He pointed out that the dose of alcohol apparently effective in "causing" cirrhosis in children is proportionally smaller than in the adult

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At the present time one may conclude that alcoholism is a common precursor of Laennec's cirrhosis of the liver, but that it is neither the only, nor necessarily the most important predisposing cause

A, C and D Forty-four of his 64 patients with portal cirrhosis with ascites were malnourished; 39 came from the lowest economic levels In Ceylon, the diet, 'lacking in nitrogenous constituents and vitamins,' on which the patients subsisted before the onset of their disease, was considered of major importance (278) A study of the diet of patients in Syria, where alcohol is unimportant as a predisposing agent in cirrhosis, showed it to be poor in proteins, and Vitamin A, with bread and legumes the staple foods (313) In a report of 84 cases with cirrhosis of the liver in China, Yang (311) observed that over 70 per cent of the cases were in the laboring class who lived on coarse carbohydrate food and who led a strenuous, muscular and outdoor life Although the above authors stress the poor dietary in the background of cirrhosis of the liver, other factors such as enteric fever, malaria, and parasitic infestations are considered by them to be of primary etiologic importance It should be noted that these same diseases would aggravate a state of nutritional deficiency

At least half of the cases of cirrhosis of the liver in this country occur in alcoholics (see Table 6) The frequent association of dietary deficiency with chronic alcoholism is now well recognized Romano (228) found that of 96 alcoholics 78 per cent had a history of an inadequate diet, which was extreme in 9 cases In a preliminary report on 13 patients with cirrhosis of the liver, Patek (191) found marked evidence of malnutrition, and specifically signs of lack of the Vitamin B complex The diets of the patients were found to be deficient in meat and dairy foods When the patients were fed a highly nutritious diet, ample in these foods and supplemented by Vitamin B concentrates the clinical improvement that followed seemed outside chance expectation These findings were confirmed and extended in a report on 54 patients observed during a four-year period (192) Similar favorable results of therapy with a nutritious diet and vitamin concentrates have recently been reported by Snell (249) in 50 cases of cirrhosis Case reports of individual patients who responded favorably to this treatment have been published by Meyers (172) Prado (204) and Richet and his collaborators (219) Connor (62) also has expressed the opinion that dietary deficiency may be a significant or predisposing factor in this disease Wayburn and Guerard (288) reviewing the association of peripheral neuritis and cirrhosis, found that 72 of 272 patients with cirrhosis, or 26 per cent had a history of a deficient diet, including 10 patients with outspoken pellagra

The rôle of diet in the etiology of cirrhosis has been the subject of a number of recent experimental studies It has long been known that starvation renders the liver vulnerable to injury (66) Recent studies indicate that the feeding of yeast (282, 138), of protein (98, 173-246), and of choline (25) may afford a degree of protection against liver poisons Other studies suggest that the lack of certain unknown factors contained in yeast brings about fibrotic changes in the livers of rats (103-104, 290, 291), and rabbits (216, 217) The feeding of excess fat (52-104, 290, 291, 25) or cystine (70, 104) and of diets low in protein (104, 291-152, 25) also are said to cause fibrotic changes in the liver of experimental animals Possibly a balance of food factors may be essential to the

which is not clear. Some cases of cirrhosis may be the result of therapy with arsenic compounds.

Coincidence of alcoholism and syphilis as a precursor of Laennec's cirrhosis

If there were a synergistic relation between alcoholism and syphilis in the causation of cirrhosis, they should co-exist oftener than could be accounted for by chance. However, if the two act as independent agents, or if either is merely an incidental finding in the background of the disease, their co-existence should follow the rôle of chance. Alcoholism occurred in 207, and syphilis in 86 of the 386 patients. Their chance co-existence should occur in 8.6 per cent of the cases (cf Table 8). Actually, 32 of the patients, or 8.3 per cent of the series, had both a history of alcoholism and evidence of syphilis. In this series, therefore, they appear to co-exist within the limits predictable by chance.

TABLE 8

Coexistence of alcoholism and syphilis in patients with Laennec's cirrhosis

	MALES	FEMALES	TOTAL NUMBER	MALES	FEMALES	PER CENT TOTAL NUMBER OF CASES
				<i>per cent</i>	<i>per cent</i>	
Alcoholism	163	44	207	61.0	36.9	53.6
Syphilis	49	13	62	18.3	10.9	16.1

Chance expectancy of coexistence of alcoholism and syphilis

$$\frac{207 \times 62}{386 \times 386} = 33.2 \text{ cases}/386 = 8.6 \text{ per cent}$$

Actual coexistence of alcoholism and syphilis

$$32 \text{ cases}/386 = 8.3 \text{ per cent}$$

Dietary history

The large majority of hospital records reported here make no mention of the patients' food intake or eating habits. Forty patients, or about 10 per cent, gave a history of a diet low in fat, protein, carbohydrate, or vitamin-containing foods. Of these 40 patients, 27 were alcoholics. In addition to these, there were 27 patients with peripheral neuritis. Assuming that these patients also had deficient diets, a total of 67 cases, or 17 per cent of the total series, gave evidence of deficient diets. These figures are probably inadequate, since a parallel study of cirrhosis (at the Research Service of the First Division of the Welfare Hospital) reveals a much higher incidence of dietary deficiency in such patients (191, 192).

Attention was first directed to the possible contributory rôle of diet in the etiology of cirrhosis in those countries where alcoholism was unimportant in the background of the disease. In India, the excessive use of condiments in the diet was first blamed for the high incidence of cirrhosis there. In a more critical recent survey by Rao (212), the diets of patients with cirrhosis in Southern India were described as usually deficient in protein, fat and vitamins, especially

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integrity of the liver. The significance of these studies in relation to human Laennec's cirrhosis awaits further confirmation and clarification.

History of previous jaundice

The history of an episode of jaundice, apparently unrelated to their present illness, was given by 25 patients, or approximately 65 per cent of this series. The nature of the jaundice was not clear. Such episodes occurred from one to 36 years before the onset of clinical cirrhosis. In two instances the jaundice was attributed to arsenic poisoning.

Soffer and Paulson (250) studied 11 patients with a history of "catarrhal jaundice" 3 months to 18 years previously, using the bilirubin excretion test. Nine of these patients showed abnormal retention of injected bilirubin. Polack (200) described 8 patients from 24 to 29 years of age who had a syndrome of "chronic hepatitis" for from 3 to 8 years following an initial episode of "acute hepatitis." These patients were chronically fatigued, had a sensation of fullness in the right side of the abdomen, and tenderness under the right costal margin. In 3 cases there was persistent slight icterus which was accentuated at times. The urine of these patients practically always contained urobilinogen or bile acids or both. During exacerbations which lasted from one to several weeks, there was slight enlargement of the liver and loss of appetite and weight. The spleen never became palpable. Polack felt that these patients were in the primary stages of cirrhosis. No biopsies were taken of any of these patients.

Carniol (48) in 1922 described a case of cirrhosis following a transient episode of jaundice indistinguishable from "epidemic jaundice." The patient had a remission, but died 5 years afterwards following an illness characterized by fever, vomiting and diarrhea. At post-mortem she was found to have atrophic cirrhosis, an enlarged spleen and peri-hepatitis and peri-splenitis. Shortly after this, Jones and Minot (133) reported 3 cases of sporadic jaundice in which the jaundice lasted for several months. At operation, cirrhosis of the liver and an inflamed biliary tract were found.

Eppinger (74) noted that 14 per cent of 269 male patients, and 12 per cent of 107 female patients with cirrhosis gave a history of an earlier "catarrhal jaundice." In Southern India, Rao (212) noted such a history in 8 of 64 patients with portal cirrhosis and ascites.

Bloomfield (24) found that 4 of 41 patients with advanced cirrhosis had a definite history of an "ancient jaundice" from 8 to 27 years before, three others gave a doubtful history, but he pointed out that patients are liable to imagine that a previous fallow complexion was "jaundice." He concluded that acute hepatitis is rarely the precursor of or an initial stage of what later develops into advanced cirrhosis. Bloomfield also noted that cases indistinguishable clinically from acute hepatitis may progress fatally with the symptoms and pathology of portal cirrhosis.

Connor (63) and Pratt and Stengel (205) reported similar series of cases, in which an episode similar to acute hepatitis marked the onset of the final illness or preceded it by several years. The usual pathologic picture was that of a

grossly deranged liver with nodules of liver cells between coarse dense connective tissue, necrosis and regeneration of liver cells were sometimes seen. Following Mallory's (160) classification, these authors classified these cases as instances of "toxic cirrhosis."

There are differences of opinion concerning the type of cirrhosis that follows acute or subacute hepatitis. Mallory has described as a separate group cases of "toxic cirrhosis" which represent healed acute or subacute yellow atrophy. In these cases the fibrosis is diffuse and generalized, involving the central as well as the portal areas. There is no doubt that certain livers conform to this description at autopsy. Others appear to be "mixed" in type. Still others, of which the *clinical* history has been that of healed yellow atrophy, reveal *histologic* findings of Laennec's cirrhosis. Whether or not "toxic cirrhosis" is an entity has been questioned by various workers. It has been shown, for example, that in experimental cirrhosis, caused by hepatotoxins such as arsenic and carbon tetrachloride, either a central or portal distribution of lesions can be produced, depending on the severity and duration of the poisoning.

In summary, a significant number (6.5 per cent) of patients with Laennec's cirrhosis gave the history of an earlier episode of jaundice. It is therefore possible that recovery from episodes of "catarrhal jaundice" or "epidemic jaundice," or "acute hepatitis" may be followed by permanent structural damage leading finally to a clinical and pathological picture indistinguishable from Laennec's cirrhosis.

History of exposure to toxic agents

A. Arsenic Thirty-six of the patients in this series were exposed to enteral or parenteral arsenic. Of these, 34 had been treated with arsphenamine or its derivatives. Two of these 34 patients were jaundiced during the period of therapy. Seventeen of the 36 patients, or 47 per cent of the series, gave the additional history of alcoholism. The chance coincidence of these two factors would be approximately 50 per cent. As with syphilis and alcoholism, therefore, their coincidence here has no significance.

In 1898 Geyer (93) reported an epidemic of arsenic poisoning at Reichenstein in Schlesien, and mentioned the frequent occurrence of ascites. Two years later there was an epidemic of arsenic poisoning in beer drinkers in the Midlands and North of England. The source of the arsenic proved to be sugars used in brewing the beer. One author in reporting this epidemic noted 'a number of cases of cirrhosis' (215). Sturrock and Brown (259) described 8 patients with "interstitial hepatitis", these had a syndrome characterized by swelling of the abdomen, pain in the right upper quadrant and in half of the cases, bloody stools. Physical examination revealed that the liver was enlarged and tender; sometimes there was icterus and ascites. These patients recovered.

Baldridge (9) reported that of 36 cases of alcoholic or toxic cirrhosis, 12 were in patients who had had treatment with arsphenamine. Two of these patients had other symptoms of arsenical poisoning. O'Leary, Snell and Bannick (185)

reviewed the literature and described two patients who had taken inorganic arsenic for several years and who had developed ascites. Bromsulfalein tests in these patients showed slight abnormal retention of the dye. Other instances of chronic liver disease due to inorganic arsenic poisoning have been reported by Hutchinson (123), Hamburger (107), Stockman (257), and Weir (292).

Von Glahn, Flinn, and Keim (281) have demonstrated in rabbits that cirrhosis of the liver may be produced by feeding small amounts of arsenates.

B Lead Nine of the 386 patients in this series were exposed to lead in their occupations. However, since seven of these were alcoholics, and since 3 were exposed to arsenicals as well, there would appear to be no evidence that exposure to lead was an etiologic factor in this group of patients.

In 1888 Potam (203) reported a case of cirrhosis in a non-alcoholic patient which he believed might have been due to lead poisoning. Böttlich (33) in 1933 described a case of cirrhosis in a patient with known lead poisoning, but he did not know whether they were causally related. Bazzano (19) reviewed the incidence of cirrhosis in lead poisoning. He found that among 500 painters with lead poisoning, 4, or 0.8 per cent, had cirrhosis. All these 4 were alcoholics, as were 217 of the 500 patients. Forty-three per cent of the patients had enlargement of the liver. Half of these patients were alcoholics, drinking a quart or more of wine each day. In a recent survey of the effect of exposure to lead arsenates on orchardists and consumers of sprayed fruits (182), no mention is made of the appearance of jaundice, ascites, enlargement of the liver or any hepatic pathology in these subjects.

In all likelihood, therefore, lead need not be considered an etiologic agent in cirrhosis in man.

C Cinchophen There was no instance of cirrhosis in this series which could be attributed to cinchophen poisoning. There are numerous reports in the literature of liver damage and cirrhosis due to cinchophen and its derivatives. These were reviewed in 1932 by Weis (295), and the following year by Weir and Comfort (293), who collected 117 cases of cinchophen poisoning with liver damage, including 61 patients who died. Weis pointed out that the toxicity of cinchophen seemed unrelated to the dose of the drug taken by the patient.

D Miscellaneous Moon (176) has reviewed the action on the liver of various toxic agents. Carbon tetrachloride is an effective agent for the production of cirrhosis of the liver experimentally (44). Peery (196) has recently reviewed the effects of carbon tetrachloride poisoning in man. Ponder and Greene (199) reported an instance of hepatic cirrhosis in man, verified at autopsy, following exposure to a cleaning mixture containing 55 per cent carbon tetrachloride. Other instances in which exposure to this chemical was followed by symptoms suggestive of hepatic involvement have been reported by Butsch (41), McGuire (166), and Lyon (156).

Chloroform, another agent producing liver injury in the experimental animal, seldom causes the disease in humans. Brunner (38) reported 2 cases in patients anesthetized with chloroform, and mentioned 2 others in the Italian

literature Brunner's patients died 3 and 5 days after anesthetization, and at autopsy were found to have cirrhosis of the liver. It seems likely that this antedated the exposure to chloroform which put an added lethal burden on the liver.

Willcox and Spillsbury (300) reported that *tetrachlorethane*, used in making a 'dope' for airplanes caused cirrhosis among factory workers exposed to its vapors. *Trichlorethane*, used in the manufacture of artificial pearls has also been reported to produce cirrhosis (80).

Willmot and Robertson (303) described a syndrome among the poorer classes of Europeans living in South Africa which included frequent hematemesis, melena, enlargement of the liver and ascites. The patients died 2 weeks to 2 years after the onset of symptoms. On pathological examination the liver was enlarged with dilation of the capillaries between the liver cells, infiltration with round cells and new fibrous tissue. Willmot and Robertson believed the syndrome was identical with *senecio*, a disease of cattle known in Nova Scotia as Pictou disease and in New Zealand as Winton's disease. *Senecio*, they believed, is due to the ingestion of the weeds *senecio ilicifolius* and *burchelli*. Recently Davidson (65) isolated the alkaloid *retrorsine* from *senecio* weed and found that it produces hemorrhage and necrosis in the liver of rats.

A number of other substances have been claimed to produce cirrhosis in humans. Among the natives of Tierra del Fuego there is a syndrome of icterus, hypertrophy of the liver followed by atrophy, and hemorrhage from mucous membranes. This was attributed (239) to the eating of mussels, which formed the major part of their diet. Cases of cirrhosis have been described in persons who habitually drank large quantities of vinegar (132-76).

Cirrhosis has been produced experimentally by a number of other agents with which humans may come in contact. Smith (247) found that 20 per cent of experimental animals given *selenium* develop cirrhosis of the liver. *Manganese* alone or in combination with chloroform, readily produces cirrhosis in rabbits (122). Since silica is found in beer, it has been accused of causing cirrhosis, but although colloidal silica causes an increase in the periportal connective tissue of the liver when repeatedly injected intravenously in rabbits, silica by mouth is non-toxic (102-92, 242). An ether- and acetone-soluble substance has been isolated from the meal of buckwheat which produces "annular cirrhosis" in dogs and mice and a non-malignant tumor of the liver in the latter animals (142). *Plenylhydrazine* used in the treatment of polycythemia vera produces hepatic cirrhosis in rabbits only inconstantly, but in combination with manganese produces cirrhosis in the guinea-pig and possibly the rabbit (122).

Small doses of *phosphorus* have long been known to produce cirrhosis of the liver in experimental animals. Mallory (158) thought that contamination with phosphorus might explain the rôle of alcohol in the pathogenesis of cirrhosis. Analysis of 25 samples of 'hard' liquor however did not reveal any contamination with phosphorus. The ingestion of *copper* was found by Mallory, Parker and Nye (161) to produce a pigment cirrhosis in rabbits, guinea-pigs,

monkeys, and sheep (162) The conflicting evidence concerning the role of copper in the etiology of cirrhosis has been reviewed by Robert (220) It is beyond the province of this article to discuss the relationship between copper poisoning and human hemochromatosis There is, however, no evidence that copper poisoning plays any rôle in the etiology of Laennec's cirrhosis in man

Recently cirrhosis has been produced by administering *furfural* to rats fed a diet of polished rice supplemented by carrots (181) Furfural is present in saké, a common alcoholic beverage in Japan Other substances present in saké did not produce cirrhosis

Diabetes mellitus

The incorrect diagnosis of Laennec's cirrhosis is made occasionally because of the presence of a palpable liver in patients with diabetes mellitus After the exclusion of such cases, together with those of hemochromatosis, there remain in our series 13 cases of Laennec's cirrhosis in which the diagnosis of diabetes mellitus was made, and 8 other patients whose tests revealed glucose tolerance curves that were characteristic of diabetes mellitus This total of 21 cases, or 5 per cent of the series, is an unexpectedly high incidence However, 9 of the patients were Jews, in whom the high incidence of diabetes mellitus has long been recognized

There are few reports concerning the coincidence of diabetes and cirrhosis of the liver Yeld (312) found in pathological material that among 131 cases of cirrhosis there were 2 patients with diabetes mellitus Among 126 patients with cirrhosis coming to autopsy, Blumenau (26) described 4 in whom the immediate cause of death was diabetes mellitus Rabl (207) noted 3 cases in which diabetes mellitus was present among 275 autopsies in which cirrhosis was present In addition, there were 21 instances of hemochromatosis in his series

In a carefully studied series of 118 cases of Laennec's cirrhosis observed *post-mortem*, Robert (220) noted that diabetes mellitus was present in 7.6 per cent of patients compared with 2.4 per cent of adult patients in whom cirrhosis was not present at autopsy Hepatic cirrhosis, however, is apparently uncommon among diabetics Wilder (301) found evidence of cirrhosis or hepatitis in only 0.7 per cent of 2,584 cases of diabetes mellitus at the Mayo Clinic He believed that "When hepatic disease was found, it seemed rarely to be related to the diabetes or to affect it seriously"

Experimental studies have been reported concerning a possible relation of pancreatic function to the development of liver cirrhosis It has been shown that ligation of the pancreatic ducts, depancreatization, or high fat feeding in dogs are followed by fatty infiltration of the liver The fatty infiltration so produced can be prevented by feeding raw pancreas, choline, or water-extracted meat powder (210) Chaikoff, Connor and Biskind (52) moreover have reported the development of portal cirrhosis in depancreatized dogs after $2\frac{1}{2}$ to 5 years Recently they succeeded in producing cirrhotic changes in the dog by high fat feeding alone (53) Since the liver of chronic alcoholics char-

acteristically has a high fat content the inference might be drawn that fatty infiltration was a necessary precursor to the development of cirrhosis. It would be premature to draw such conclusions at the present time. The cirrhosis produced experimentally by selenium and by cystine is not correlated with fatty infiltration. The relation (if it exists) of pancreatic function to fatty infiltration, and in turn of fatty infiltration to cirrhosis of the liver is not clearly established.

There are a number of cases reported in the literature in which, with the development of cirrhosis of the liver a pre-existing diabetes mellitus was ameliorated (32, 258). The converse, in which regulation of diabetes in a patient with cirrhosis was accompanied by a remission of the latter disease likewise has been described (164, 112).

History of thyroid disease

Moon (176) directed attention to a parallel between the death rate from thyroid disease and from cirrhosis of the liver. He pointed out that the highest incidence of cirrhosis in Europe is in Switzerland, where goitre is prevalent. However in the present series there were but 4 cases of goitre in 386 cases of cirrhosis. Of these, 3 were non-toxic, the fourth had hyperthyroidism coincident with cirrhosis of the liver. Among 112 patients with cirrhosis of the liver and ascites at the Mayo Clinic (54), 2 had hyperthyroidism. These findings suggest a low incidence of thyroid disease in patients with cirrhosis of the liver in this country.

Nevertheless there is substantial evidence that thyroid disease, specifically hyperthyroidism, may lead to diffuse liver damage and cirrhosis. Impaired liver function has been reported by a number of workers (314, 151, 15, 157). Others have demonstrated evidence of liver damage at histological section. Beaver and Pemberton (20) reported autopsy findings on 107 cases of exophthalmic goitre. A significant number of these cases had either acute degenerative lesions of the liver or cirrhosis. Similar findings have been recorded by Habán (105), Cameron and Karunaratne (45), Bartels and Perkins (14) and more recently by Shaffer (241).

It can be concluded that in hyperthyroidism there is frequent impairment of liver function and in fatal cases, a rather high incidence of cirrhosis of the liver. Speculation over the mechanism whereby hyperthyroidism leads to liver damage would be premature at this time. Cases of hyperthyroidism, however, can account for only a small percentage of cases of cirrhosis.

History of malaria

A past history of malaria was obtained from 33 patients, or slightly less than 9 per cent of this series. At first thought, this high incidence was attributed to the large number of Italians and Greeks with cirrhosis. However, this explanation is not supported by a study of the racial distribution of these cases (cf Table 9).

The rather frequent background of malaria in cirrhosis has been the subject

of much debate Chapman, Snell and Rowntree (54) found that 11 per cent of 112 patients with cirrhosis and ascites gave a past history of malaria The proportion is much higher in those countries where malaria is common place, reaching as high as 84 per cent in one large Indian series (260)

Osler (189) wrote, "The cirrhosis from malaria upon which French writers lay so much stress (one described 13 varieties!) is exceedingly rare In our large experience with malaria during the past 15 years, not a single case of advanced cirrhosis due to this cause has been seen in the wards or autopsy room at the Johns Hopkins Hospital" Trumurti and Rao (274) reviewed the rôle of malaria in cirrhosis, and made a study of the pathology of the livers of patients with chronic malaria They found that there was no loss of lobular pattern, and no increase in the fibrous tissue of the liver The Kupfer cells were loaded with malarial pigment, and there were sporadic degeneration and

TABLE 9
Historical incidence of malaria in patients with Laennec's cirrhosis

RACE	NUMBER OF CASES
U S	7
Irish	6
Italian	6
Greek	5
Jewish	2
Negro	2
Armenian	2
Spanish	1
Puerto Rican	1
Barbados White	1
Total	33

focal necroses of the hepatic cords inconstantly They concluded that there was no evidence from pathologic material that malaria produced cirrhosis

Malaria is thus a frequent factor in the background of patients with cirrhosis of the liver, but there is no evidence that it plays a direct rôle in its etiology

History of typhoid fever

Fifteen patients in this series gave a history of typhoid fever Since so many of the patients lived during the time when typhoid fever was endemic, it is probable that this number is no larger than would be expected from any similar age group In Chapman, Snell and Rowntree's series (54) of 112 cases of "decompensated" cirrhosis, 18 patients gave a history of typhoid fever

History of tuberculosis

Four patients in this series gave a history of tuberculosis, and 4 others had active tuberculosis during the course of their cirrhosis

This low incidence of tuberculosis has been noted by recent American writers

Evans and Gray (75) found 6 cases of active tuberculosis among 217 patients found to have cirrhosis at post-mortem, and McCartney (165) reported 3 cases of active tuberculosis among 158 patients with portal cirrhosis at autopsy.

Earlier, however, when tuberculosis was more prevalent than it is today, it was frequently seen in association with cirrhosis. Of Osler's 71 cases of cirrhosis (189), 7 had active tuberculous peritonitis or tuberculous pleurisy. In England, the incidence of tuberculosis among patients with cirrhosis is high. Rolleston and Fenton (226) reported in 1896, that among 114 patients who had cirrhosis at autopsy, 17 died of tuberculosis, and 17 others had tuberculosis which was not the cause of death. Elsewhere, the incidence is even higher. Sison, Sison and DeLeon (243) found that 31 per cent of clinical cases of portal cirrhosis in the Philippine Islands had pulmonary tuberculosis. Roch and Wohlers (221) found in pathologic material that 35 per cent of 431 patients with cirrhosis in Geneva, between 1900 and 1930, had active tuberculosis. Rabl (207) made an extensive review of the literature concerning the coincidence of cirrhosis and tuberculosis. He pointed out that although tuberculosis was frequent in European patients with cirrhosis, it was not more frequent than in numerous control series.

In summary, tuberculosis seems to be less frequent in this series than has been reported by most previous observers. It is probable that the low incidence of tuberculosis is due to the general decline in the incidence of tuberculosis, particularly abdominal tuberculosis, in the last generation.

History of chronic dysentery

Only 6 of 386 patients with cirrhosis of the liver in this series gave a history of chronic dysentery. In series of cases of cirrhosis reported from India (225, 168, 212), China (287), and the Philippines (243), the incidence of dysentery ranges from 25 to 40 per cent compared with control series with 7 to 17 per cent of dysentery. Nevertheless, Tirumurti and Rao (275) could find no evidence at necropsy of active or old bacillary dysentery in the intestines of 18 patients found to have portal cirrhosis at autopsy in Southern India.

It was stated previously, on the basis of certain clinical and experimental observations, that nutritional deficiency may be a determining factor in the etiology of cirrhosis of the liver. If this evidence proves correct, then it would serve to explain the common association of cirrhosis with enteric diseases and protracted fevers in the Orient. These diseases undoubtedly impair the nutrition of the patients. Such impairment would be particularly grave in patients who are ill-fed.

Other infectious agents

A number of specific infectious agents have been claimed to be the cause of human cirrhosis. Adam (3) in 1898 believed he had isolated a diplococcus or stumpy diplobacillus from the liver of cattle dying from Pictou disease, a form of cirrhosis identical with senecio poisoning in man. This organism was pathogenic for rabbits, guinea-pigs and mice but did not produce cirrhosis. Adam

found the organism within the liver in 20 cases of cirrhosis in man, and described it as "resembling" the colon bacillus, which he found in normal livers. Pictou disease has since been found probably to be due to the toxic action of retrorsine, an alkaloid found in the senecio weed upon which the cattle feed (65). Moon (175) has also found cocci in the liver of human patients with cirrhosis.

Opie (186) observed that certain human cases with bacterial infections of the liver showed mid-zonal necrosis of the liver. He could reproduce this picture in experimental animals by combining bacterial infection with chloroform or phosphorus poisoning, and he concluded that infection could "influence or even

TABLE 10
Diseases precedent to or concomitant with Laennec's cirrhosis

DISEASE	NUMBER OF CASES	PER CENT INCIDENCE
Syphilis	62	16.1
Malaria	33	8.6
History of pneumonia	29	7.5
Hypertension and nephritis	25	6.5
Inguinal hernia	16*	6.4*
Diabetes mellitus	21	5.4
Rheumatism	16	4.1
Typhoid fever	15	4.0
Peptic ulcer	14	3.6
Cholecystitis	12	3.1
Tuberculosis	8†	
Neoplasm, not primary in liver	6	
Chronic dysentery	6	

Also 5 each—pleurisy, allergies, 4 each—goitre, renal calculus, 2 each—pernicious anemia, hydrocele, diaphragmatic hernia, erysipelas, psoriasis, filariasis, 1 each—polycythemia vera, sickle-cell anemia, silicosis, osteogenesis imperfecta, osteomyelitis, Paget's disease, mastoiditis, yellow fever, typhus, meningococcus meningitis, lymphogranuloma venereum, leprosy, dengue fever, Kaposi's syndrome, epilepsy, thromboangitis obliterans, cataract, schistosomiasis, infestation with "tape worm," with *dibothriocephalus latus*, with *tinea saginata*.

* Calculated for 248 patients only.

† 4 active, 4 inactive—see Table 20.

determine the development of cirrhosis of the liver." Hurst and Hurst (122) were also able to produce cirrhosis experimentally in guinea-pigs by combining the injection of manganese and *B. coli*.

Recently Andersen and Tuhmus (6) studied the effects of chronic infection with a virus which is thought to cause an epidemic hepatitis. Young pigs were kept on a "quantitatively poor but qualitatively good" diet for 10 days. They were then given the duodenal juice of human beings ill with epidemic hepatitis, or the liver from pigs ill with acute jaundice. The pigs were then kept for 9 to 10 months on an ordinary diet, after which period they were sacrificed. The livers were found to have a finely granular surface with some perihepatitis. On histologic examination they showed thickening of the connective tissue of the

septa, which were infiltrated with mononuclear cells. The periportal connective tissue was increased in amount. There were slight changes in the liver cells. Andersen and Tuhmus believed that the animals had developed minimal cirrhosis.

At the present time it is impossible to determine whether bacterial or virus infections play a causal role in Laennec's cirrhosis. The relatively low incidence (6.5 per cent) of acute hepatitis in the past history of the present series of 386 cases suggests that infection is of minor etiologic significance in this disease.

In Table 10 are listed the various diseases that either preceded or accompanied the onset of Laennec's cirrhosis in this series of cases.

Latent cirrhosis

The present series of 386 cases represents patients who showed clinical signs of liver failure. In addition, there were 49 patients in whom Laennec's cirrhosis was an incidental finding either at operation or at autopsy. These cases may be described as instances of "latent cirrhosis." The above figures, however, do not indicate accurately the relative incidence of latent and active cirrhosis. Rolleston and McNee (227) reported that of 167 cases of cirrhosis seen at post-mortem, 87, or 52 per cent had been latent during life. McCartney (165) reported that among 245 autopsied cases of portal cirrhosis, 35 per cent had been latent. Thus, about one-third to one-half of the cases of cirrhosis are asymptomatic or latent.

These authors reported that the average age at death was approximately the same for active and latent cases. As pointed out by McCartney, there is no evidence that more advanced degrees of cirrhosis occurred in the older patients. From this he inferred that the cirrhotic process can be arrested and that the disease is not necessarily committed to a progressive course. This interpretation is supported by experimental and clinical studies. In the dog, and in the rat with carbontetrachloride cirrhosis, considerable healing and regeneration of liver tissue take place. Likewise, in certain patients with decompensated Laennec's cirrhosis functional improvement has been observed following treatment with a highly nutritious diet (191,192).

SYMPTOMS OF LAENNEC'S CIRRHOSIS

The symptoms of Laennec's cirrhosis in 386 patients are listed in Table 11 in their order of frequency. This table comprises symptoms that arose at any time during the course of the disease. These will be discussed in detail.

Symptoms at onset

The initial symptoms and signs of Laennec's cirrhosis in the above series are presented in Table 12. The most common first symptom was the insidious onset of *swelling of the abdomen*, which occurred in more than one-fourth of the patients. This is usually painless, but may be accompanied by either abdominal pain or distress. Sudden *hematemesis*, with no premonitory signs other than perhaps vague gastro-intestinal discomfort and nausea for a few hours preceding

the episode, signalled the onset in about 10 per cent of the cases. *Abdominal pain*, generalized or localized to the right upper quadrant or epigastrium, was the earliest manifestation of the disease in 12 per cent of this series. In 9 per cent of the cases, the patient first noticed the presence of *swelling of the lower ex-*

TABLE 11
Symptoms of Laennec's cirrhosis in 386 patients

SYMPTOM	NUMBER OF CASES	PER CENT OF CASES
Weight loss	206	53.4
Anorexia	135	35.0
Nausea	129	33.4
Pain	121	31.4
Vomiting	115	29.8
Hematemesis	106	27.4
Nocturia	103	26.6
Hemorrhagic phenomena	99	25.6
Dyspnea	82	21.2
Weakness	82	21.2
Diarrhea	78	20.2
Abdominal distress	63	16.3
Cough	35	9.1
Constipation	33	8.5
Frequency	27	7.0
Eructation	25	6.5
Fatigue	15	
Pruritus	13	
Malaise	12	
Melena without recorded hematemesis	9	
Cramps in legs	9	
Oliguria	8	
Insomnia	8	
Palpitation	7	
Amenorrhea	6	
Joint pains and swellings	6	
Backache	6	
Abdominal mass	5	
Headache	5	
Dizziness	5	
Polydipsia	5	

Also 4 each—substernal pain, 3 each—menorrhagia, metrorrhagia, precordial pain, dysphagia, 2 each—hiccough, irregular or scanty menses, paresthesias, 1 each—loss of libido, miscarriage, blurred vision, numbness, polyuria

tremities, though it is possible that in many of these cases ascites was already present but unrecognized. In 9 per cent of the patients in this series, *jaundice* was the first symptom noted. *Nausea* and *vomiting*, *weakness*, and *abdominal distress* were of common occurrence. Among the rare symptoms, an onset marked by chills and fever in 3 patients is of note. In 46 cases the onset was marked by several symptoms.

Murchison (179) in 1877 characterized the early symptoms of cirrhosis as 'alcoholic dyspepsia such as retching in the morning and a feeling of sinking inducing a craving for alcohol, loss of appetite for solid food, furred tongue bitter taste flatulence, and pain after food attacks of diarrhea, alternating with constipation hemorrhoids, the urine dark and frequently turbid with lithates and sometimes containing bile-pigments and langour with depression of spirits Osler (189) noted that the patient might come to the doctor because of dyspepsia, hematemesis, slight jaundice, or nervous symptoms Meteorism may appear early in the disease (118)

TABLE 12
Initial symptoms and signs of Laennec's cirrhosis

Symptom	NUMBER OF CASES	PER CENT OF CASES
• Swollen abdomen	107	27.7
• Abdominal pain	48	12.4
• Hematemesis	39	10.1
• Edema of lower extremities	36	9.6
• Jaundice	34	8.8
• Nausea and vomiting	29	7.5
• Weakness	22	5.7
• Abdominal distress	17	
• Bleeding, epistaxis	15	
• Diarrhea	14	
• Anorexia	9	
• Weight loss	7	
• Dyspnea (in absence of ascites)	6	
• Abdominal mass (liver or spleen)	5	
• Melena (without hematemesis)	4	
• Cough	4	

Also 3 each—chills and fever, pruritus, fatigue, constipation 2 each—hemorrhoids, amenorrhea, malaise, fever 1 each—umbilical hernia splenomegaly dark urine, purpura, nocturia, pallor, joint pains, polyuria, abdominal tenderness, metrorrhagia, back-pain, inguinal pain, oliguria, dysphagia, insomnia

Multiple symptoms 46

Hughson (121), studying 26 patients with cirrhosis noted that the onset of the disease was marked by acute abdominal pain in 8 patients by swelling of the abdomen in 13 and by hemorrhage from the gastro-intestinal tract in 3

Gastrointestinal symptoms

It is evident that those symptoms referable to the gastrointestinal tract were prominent For the sake of clarity these are grouped in Table 13 An early and characteristic symptom of cirrhosis is *anorexia* Present in at least 35 per cent of the patients in this series, it is usually profound Anorexia in cirrhosis was ascribed to 'alcoholic' gastritis by Saundby (231) This was corroborated by Askanazy (7) who found that 42 of 64 patients with "alcoholic cirrhosis had evidence of "alcoholic gastritis on examination at autopsy It

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Cramps in legs	9	
Oliguria	8	
Insomnia	8	
Palpitation	7	
Amenorrhea	6	
Joint pains and swellings	6	
Backache	6	
Abdominal mass	5	
Headache	5	
Dizziness	5	
Polydypsia	5	

Also 4 each—substernal pain, 3 each—menorrhagia, metrorrhagia, precordial pain, dysphagia, 2 each—hiccough, irregular or scanty menses, paresthesias, 1 each—loss of libido, miscarriage, blurred vision, numbness, polyuria

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is likely, however, that the presence of a distended abdomen resulting from flatulence or the accumulation of ascitic fluid is a large factor in the production of anorexia

Characteristically, there is a rapid *loss of weight and flesh* which may be masked by the presence of ascites and edema. Of 206 patients who had loss of weight in this series, 158 showed this in spite of the presence of ascites. Eppinger (74) described "loss of flesh" in 42 per cent of 372 patients with cirrhosis, and 44 of Rao's 64 patients (212) who had cirrhosis with ascites were emaciated.

Nausea and vomiting are prominent early symptoms, present in approximately 30 per cent of the patients in this series. *Excessive eructation* occurs frequently. "Dyspepsia," Rolleston and McNee (227) wrote, is an almost constant finding in cirrhosis. Nausea and vomiting were frequent in their experience. Eppinger (74) emphasized that these symptoms are particularly prominent when the patient awakes, early morning nausea and vomiting being present in 37 per cent of his 372 cases.

TABLE 13
Gastro-intestinal symptoms in Laennec's cirrhosis

SYMPTOM	NUMBER OF CASES
Weight loss*	206
Anorexia	135
Nausea	129
Vomiting	115
Diarrhea	78
Abdominal distress	63
Constipation	33
Excessive eructation	25

* Refers to over-all weight, including ascites in 158 cases

A change in bowel habit took place in about one-fourth of the patients in this survey. *Diarrhea*, which lasted for varying periods of time, occurred in 78 of the patients, and *constipation* in 33. Diarrhea was present in 32 of 112 patients who had cirrhosis with ascites studied at the Mayo Clinic (54). Forty-one of the patients had constipation. Rolleston and McNee (227) pointed out that patients with cirrhosis may have alternate bouts of diarrhea and constipation. *Flatulence* was described by Chapman, Snell and Rowntree (54, 55) in 33 of 58 patients who had cirrhosis without ascites, and in 60 of 112 patients with ascites. An early symptom of cirrhosis, it contributes to the swelling of the abdomen so frequently present.

Abdominal pain

Abdominal pain was present at some time during the course of 121 patients, or 31 per cent of this series. The pain was generalized in 32 instances, localized to the right upper quadrant 37 times, and localized to the epigastrium 29 times. The pain was described as sharp, or less frequently as cramp-like. Only occasionally was tenderness associated with abdominal pain.

Nissen (183), reviewing the history of 77 patients who were observed to have 'alcoholic cirrhosis at autopsy, noted that pain was described during the course of the disease in 30 instances. The pain was either constant or remittent and lasted from a few days to 8 years. In 13 patients the pain was localized to the right hypochondrium, in 8 to the epigastrium and in 6 there was generalized abdominal pain. In 8 of the patients who had right hypochondriac pain, this symptom preceded the appearance of either jaundice or ascites.

Henrikson (115), who found that 82 of 162 patients with cirrhosis complained of abdominal pain or distress attributed the pain to three possible causes, occlusion of the mesenteric vessels, intermittent vascular spasm and perisplenitis. There has been no evidence to support or refute any of these possibilities. However, a *frictio rubra*, audible and palpable over the liver itself in patients who have cirrhosis with ascites was described by Jackson (126), this may account for some instances of abdominal pain.

Hematemesis

Hematemesis occurred in 106 patients, or 27 per cent of the series. Fifty-five of these patients died following the episode. Of these 55, 22 had survived a previous hematemesis while 33 succumbed to the initial attack. There were therefore 73 patients who survived an episode of hematemesis.

The occurrence of hematemesis in 27 per cent of the present series and in 24 per cent of a small group (192) agrees roughly with the incidence in other series. In Henrikson's (115) series of 162 cases, 39 (24 per cent) had hematemesis. However, in Wang's (287) series of 54 cases, only 5 (9 per cent) had hematemesis. Eppinger (74) reported that 8 per cent of patients with cirrhosis in his series had hematemesis. He states (73) that approximately 10 per cent of deaths from cirrhosis are due to ruptured varix, which is considerably lower than our figure of 26 per cent.

In 15 patients in whom studies were made, there was a rise to abnormal levels of the plasma urea-nitrogen or non-protein nitrogen. Twelve patients were noted to have a temperature of more than 100.4° F. The cause of azotemia following gastrointestinal hemorrhage has been the subject of investigation in recent years (233-130). It is generally accepted that the rise in blood urea is due in part to the absorption of nitrogenous products from the blood, and possibly also to impairment of renal function.

Occasionally ascites appears after an episode of hematemesis, only to recede as the patient recovers from the blood loss. In three patients personally observed (but not included in this series) the appearance of ascites directly after hematemesis was associated with a fall in the serum albumin to less than 3 grams per 100 cc. Remission of ascites occurred as the serum albumin rose above this value. In each patient these phenomena recurred several times with repeated hemorrhages.

Although *melena* regularly follows hematemesis there were 9 patients in whom *melena* was described in its absence. This *melena* may have been due to slow leakage from an esophageal varix, bleeding hemorrhoids or a generalized hemorrhagic tendency. It may be emphasized that much bleeding may take

place in the upper gastrointestinal tract, and indeed from esophageal varix, without hematemesis

Most observers agree that hematemesis in patients with cirrhosis usually is the result of ruptured esophageal varix. Others have questioned this assumption because of the frequent inability to locate a bleeding point at autopsy. Preble (206) in 1900 reviewed 60 cases of fatal hematemesis in cirrhosis which had been recorded up to that time. Esophageal varices were noted in 35 of 42 cases in which the esophagus was examined. Preble believed that fatal hematemesis might occur in the absence of esophageal varices as the result of the "simultaneous rupture of many gastro-intestinal capillaries." According to Rolleston and McNee (227) hematemesis may rarely be the result of rupture of a gastric varix.

In the authors' opinion, the failure to establish the locus of hemorrhage is not surprising when the vast size of esophageal varices seen by X-ray is compared with their collapsed state *post-mortem*. The sudden, large amounts of blood lost by hematemesis seem best explained by the rupture of a large vessel. Occasionally, such hemorrhage has proved to be the result of co-existing peptic ulcer in patients with cirrhosis.

As we have noted, hematemesis is often the earliest symptom of Laennec's cirrhosis. Preble (206) observed that in 10 of 60 cases of fatal hematemesis in cirrhosis, hemorrhage was the first and only symptom, 5 of these patients dying of the initial attack.

Hematemesis is thus a frequent symptom of cirrhosis. The initial episode is fatal in as many as one-third of the cases. Hematemesis is usually the result of the rupture of esophageal varices, although these cannot always be demonstrated. Following an hematemesis, there may be a rise in the blood non-protein nitrogen, and an elevation of body temperature.

Hemorrhagic phenomena

Hemorrhagic phenomena were present in 99 of the 386 patients in this series. Seventy patients had *epistaxes*, and 33 *purpura*, of these, 12 patients had both symptoms. One child had a nose-bleed so severe that he died of exsanguination. In the great majority of cases the bleeding and clotting time were normal. Except in rare cases there was no decrease noted in the number of blood platelets. The frequency of the various bleeding phenomena in Laennec's cirrhosis is cited in Table 14.

Epistaxis, a common symptom in cirrhosis, is mentioned in early descriptions of the disease (195). Nissen (183) noted a history of epistaxis in 4 of 77 patients observed to have "alcoholic" cirrhosis at autopsy. Probably these figures understate the facts. In a recent report (192) on 54 patients with cirrhosis of the liver, recurrent nose bleeds were experienced by 25 patients (46 per cent).

Hemorrhagic phenomena in cirrhosis have not been extensively studied. Roch and Wohlers (221) reviewed 431 cases of cirrhosis observed at autopsy, and noted that 43 per cent of these had purpura, gingival hemorrhages or prolonged coagulation time. In a study of portal cirrhosis, King (140) reported

that the bleeding time was abnormally prolonged in 2 of 13 patients, and the clotting time in 11 of 36 patients. There was no significant correlation with the presence of jaundice.

The number of blood platelets in patients with cirrhosis is usually within normal limits. Two per cent of Eppinger's (74) patients with cirrhosis had thrombopenia. Fellingner and Klima (78) observed that one of 70 patients with cirrhosis had only 20,000 platelets per cubic millimeter of blood.

Interest in this subject has been revived with the investigations of prothrombin and its precursor Vitamin K (245, 30). It has been shown that the prothrombin concentration in the blood depends upon the integrity of the liver and that liver damage is followed by corresponding impairment of prothrombin production (245). Therefore, in the presence of cirrhosis, the administration of Vitamin K brings about slight, if any, increase in the concentration of prothrombin (305, 198). It is also likely that vascular spiders (193), especially when they are present in mucous membranes, provide a bleeding site in certain cases. The plasma fibrinogen concentration is seldom reduced except in cases

TABLE 14
Bleeding phenomena in 386 patients with Laennec's cirrhosis

DESCRIPTION	NUMBER OF CASES
Epistaxis	70
Purpura	33
Bleeding gums	17
Menorrhagia	3
Metrorrhagia	3
Petechiae	2
Total (excluding multiple symptoms)	99 (25.6 per cent)

of acute yellow atrophy (296, 299). It is possible that associated scurvy could account for instances of bleeding gums or purpura. Adequate study of this possibility has not been made.

In summary, bleeding phenomena occur in a significant number of patients with cirrhosis of the liver. The hemorrhagic diathesis may be explained in part by the low concentration of prothrombin, by the presence of abnormal blood vessels (spiders) in the mucous membranes, or possibly by a tendency towards thrombopenia.

Cardio-respiratory symptoms

After excluding those in whom an anatomic lesion unrelated to Laennec's cirrhosis was present, there remain a large group of patients who had cardio-respiratory symptoms. Eighty-two of the 386 patients complained of *dyspnea*. In 53 instances this symptom was noted following the appearance of *ascites*. *Dyspnea* was described by Rao (212) in 53 of 64 patients who had cirrhosis with *ascites*, and Henriksen (115) noted *dyspnea* in 14 per cent of 162 patients with

cirrhosis Theirfelder (270) in 1878 attributed the dyspnea to distention of the abdomen, "the peritoneal transudation and the inflated intestine tending to force powerfully upward the diaphragm, and interfere with its contractility. Now and then, also, hydrothorax contributed to the dyspnea."

Persistent *cough* was noted by 35 patients. It is the impression of the authors that patients with cirrhosis are susceptible to respiratory infections, due possibly to their general weakness and to the relative immobility of the diaphragm in the presence of ascites.

Urinary symptoms

Increased *frequency* of urination or *nocturia* were present in 130, or 34 per cent of the 386 patients in this series. Twenty-three of these patients were said not to have ascites at the time these symptoms were noted. Data on other urinary symptoms in this series are inadequate. Parallel studies at the Research Service of the First Division of the Welfare Hospital indicate that *oliguria*, as Austin Flint (83) pointed out, is frequent in patients with cirrhosis, particularly during the accumulation of ascitic and edema fluid.

Nocturia was noted in 48 of 162 patients with cirrhosis studied by Hennikson (115). Jervell (128) described the occurrence of nocturia in 26 patients with liver disease, including hepatitis, cirrhosis of the liver, and primary carcinoma of the liver. He attributed the nocturia to a disturbance of the "rhythmic function" of the liver in its capacity to regulate the water balance. Gilbert and Lereboullet (94) observed that in patients with cirrhosis there is a delay, compared with normal subjects, in the excretion of ingested water. This "opsiuria" they explained on the basis of retarded absorption of water from the gastrointestinal tract. This in turn was considered to be due to the hypertension in the portal system. The relation of the liver to water balance will be discussed in the chapter on edema.

Sexual disturbances

Disturbances of the menstrual cycle in women who have not yet reached the menopause are common. *Amenorrhea* or *oligomenorrhea*, described in only a few patients in this series, have been observed commonly in women of pre-menopausal age in a parallel series at the Research Service of the First Division of the Welfare Hospital.

Studies on the relationship between cirrhosis of the liver and the sexual functions are few and not definitive. *Oligomenorrhea* or irregular menses were described by Eppinger (74) as early symptoms of cirrhosis in one-fourth of his cases. Rolleston and McNee (227) believed that *metrorrhagia* is frequent early in the disease, followed later by amenorrhea. Austin Flint (84) described a girl, 20 years of age, who was observed to have cirrhosis at autopsy. She had "an undeveloped sexual system including mammae" and never menstruated. The ovaries showed no corpora lutea, and the uterus was extremely small. A very similar case was reported by Barker (11). Hartwell and Johnson (114) described a young girl found to have cirrhosis at operation, in whom remission

of ascites occurred coincident with the onset of menses in her 21st year. Cirrhosis of the liver is not incompatible with successful pregnancy. Tenney and King (267) reported the case of a woman known to have cirrhosis who was delivered of a child by Caesarian section under spinal anesthesia. They discovered two cases in the literature in which cirrhosis was first noted during the course of pregnancy.

In males, *impotence* is frequent (74). At autopsy, *fibrosis or atrophy of the testes* is common. Henschen and Bruce (116) observed testicular fibrosis in 16 of 81 cases of Laennec's cirrhosis, and testicular atrophy in 8 instances. The voluminous foreign literature concerning the incidence of *gynecomastia* in cirrhosis was reviewed in 1934 by Bergonzi (22). He collected 101 cases in Italian literature since 1864. Eighteen of these patients had associated hypotrophic or atrophic genitalia. There are no instances of gynecomastia in the present series. The only reports in the American literature of the coincidence of gynecomastia and cirrhosis are those of Edmondson, Glass and Soll (71, 95). They observed that testicular atrophy was present in each of 14 patients with liver disease, and gynecomastia in 8 instances. Endocrine assay showed that the urine androgen was below normal. Estrogen, normally excreted in combined form, was excreted in the free state in patients with cirrhosis. This they attributed to the failure of the liver to inactivate the estrogen.

One patient in the present series claimed to have lost body hair during the course of his disease. This was described in 4 of 7 women who had cirrhosis by Laignel-Lavastine, Troisier and Boquien (143), who believed that this was a manifestation of ovarian insufficiency. Loss of axillary hair during the course of cirrhosis was also observed by Jacob (125).

Sexual disturbances are therefore relatively common in Laennec's cirrhosis. However, the pathogenesis of these disturbances has not been clarified.

PHYSICAL SIGNS OF LAENNEC'S CIRRHOSIS*

The chief signs of Laennec's cirrhosis among 386 patients are listed in Table 15.

Ascites

Ascites, the most frequent and most characteristic sign of cirrhosis of the liver, was present in 301 of 386 patients, or 78 per cent of this series. In 220 instances, the ascites was associated with edema of the lower extremities, usually preceding the latter in time of appearance. Sixty-four patients, or one-sixth of the 386, had both ascites and hematemesis during the course of the illness.

Studies of Loeb, Atchley and Palmer (154) have demonstrated conclusively that ascitic fluid in cirrhosis of the liver bears the characteristics of a transudate. Rarely, as in one proved case in this series, the ascitic fluid may be chylous. Wallis and Schölberg (286) collected 28 cases of cirrhosis in the literature in which chylous ascitic fluid was present. In 13 instances free fat was demonstrated in

* Only casual reference will be made in this paper to laboratory data and to function tests of the liver. This subject has been reviewed fully by other authors.

the ascitic fluid In those cases in which examination was made, the thoracic duct was usually not obstructed

Rolleston and McNee (227) and Eppinger (73) both mention hemorrhagic ascitic fluid as a rare complication of Laennec's cirrhosis

TABLE 15
Physical signs of Laennec's cirrhosis in 386 patients

PHYSICAL SIGN	NUMBER OF CASES	PER CENT OF CASE
Ascites	301	78 0
Palpable liver	291	75 4
Jaundice	252	65 3
Edema	236	61 1
Palpable spleen	170	44 0
Hemorrhoids	105	27 2
Fever without apparent cause	93	24 5
Dilated veins	91	23 6
Telangiectasia	67	17 4
Spider angiomata	58	15 0
Peripheral neuritis	40	10 4
Varicose veins	37	9 6
Hyporeflexia	32	8 3
Absent deep reflexes	29	7 5
Hydrothorax	25	6 5
Scanty body hair	25	6 5
Pigmentation over shins	22	5 7
Clubbed fingers or curved finger-nails	21	5 4
Cyanosis	19	
Umbilical hernia	17	
"Liver palms"	16	
Inguinal hernia	14	
Hyperactive deep reflexes	14	
Generalized pigmentation	10	
Clay-colored stools	7	
Toxic delirium	7	
Tremor	6	
Hypesthesia	5	
Caput medusa	4	

Also 3 each—mania, delirium tremens, drowsiness, incarcerated umbilical hernia, 2 each—pigmentation of hands, scaly shins, irrationality, absent vibratory sense, hoarseness (without pathology), bleeding spider angiomata, 1 each—pigmentation of face, Korsakow's syndrome, hallucinations, delusions, euphoria, stupor, "psychosis," convulsions, "hysterical psychosis," carpo-pedal spasm, optic neuritis, loss of sphincter control

The many reports in the literature citing the incidence of ascites in cirrhosis are in agreement with the present survey Rolleston and McNee (227) reported that of 80 patients examined *post-mortem*, whose death was due to cirrhosis, 85 per cent had ascites In Klopstock's (141) series of 250 cases of cirrhosis studied at autopsy, 69 per cent were found to have ascites De Josselin de Jong (69) noted ascites in 57 per cent of 200 cases of cirrhosis studied at autopsy

The association of ascites with disease of the liver was first recognized by Erasistratus (c 310-250 B C) (50). Morgagni (177) believed that the ascites was due in part to obstruction of the portal vein. Describing a patient with cirrhosis he wrote "It is unquestionable that as the enlargement and disorganization of the liver advanced, the quantity of fluid effused into the abdominal cavity became more redundant. The circulation of blood through the vena portae and the inferior vena cava must have been impeded. An excess of fluid would be deposited in the abdominal cavity from mere congestion of blood. The scirrhus state of the liver also contributed to this effect. Neither healthy chyle nor healthy blood could be prepared under these circumstances."

Hypertension in the portal system in patients with Laennec's cirrhosis with splenomegaly was demonstrated by direct readings of splenic vein pressure by Thompson, Caughey, Whipple and Rousselot (271, 272). In 7 cases the splenic vein pressure ranged from 225 to 470 mm. of saline in 5 instances the pressure was 325 mm. or higher. In 19 of 20 control patients the splenic vein pressure was less than 300 mm. of saline. Since the pressure within the splenic vein and portal vein is approximately equal, this is direct evidence that in Laennec's cirrhosis there is elevation of the portal vein pressure. The presence of a collateral circulation between the portal and systemic circulations has long been recognized as indirect evidence of the presence of portal hypertension. McIndoe (167) demonstrated that it required much more pressure to inject the portal vein of a liver showing cirrhosis *post-mortem* than a normal liver.

As Morgagni predicted (177) however, purely mechanical factors cannot account for the production of ascites. Fiessinger (81) pointed out that ascites appeared in acute liver disease apparently before sufficient pathologic changes had occurred to produce portal hypertension. In addition to the increase in portal vein pressure, there is a reduction in the colloid osmotic pressure of the blood serum. In 1928, Starlinger and Winands (255) showed that with the development of ascites in a patient with cirrhosis of the liver, the serum albumin fell from 4.1 grams to 2.2 grams per 100 cc. Myers and Keefer (180) found that in every one of 16 patients with cirrhosis of the liver (including 15 with ascites) the serum albumin was 2.63 grams per 100 cc. or less. In addition to the decline of the serum albumin in cirrhosis, there is usually an elevation of the serum globulin. This was first observed in 2 patients with hypertrophic cirrhosis by Fihnski (82). Abram and Wallach (2) noted that in 13 of 15 patients with cirrhosis the serum globulin was elevated above 3.2 grams per 100 cc. and Wallach (285) reported that in 22 of 32 cases of cirrhosis the serum globulin was elevated to 4.0 grams per 100 cc. or higher. Since there is a fall in the level of serum albumin and a rise in the serum globulin the total serum protein level is only moderately affected (184). Because of the smaller size of the albumin molecule, it exerts a proportionately greater effect on the colloid osmotic pressure than the globulin molecule. As a consequence, the reduction in the level of serum albumin in cirrhosis results in a decrease in the colloid osmotic pressure of the serum.

Recent studies by Post and Patek (202) have further demonstrated a correlation between the level of the serum albumin and the presence or absence of ascites. They showed that there is a critical level (3.1 ± 0.2 grams per 100 cc) of serum albumin at which diuresis and the loss of ascites take place.

It is not implied that a reduction of serum albumin is the only cause of ascites formation. It is likely, indeed, that portal vein hypertension plays a contributory part. However, the degree of fibrosis in the liver (and presumably the portal pressure) must vary considerably in different cases. If portal hypertension were the sole cause, there should be no correlation between the presence of ascites and the level of the serum albumin, such as was observed. There are many cases with evidence of portal hypertension, yet free of ascites. Moreover, it seems unlikely that anatomical changes in the liver could take place rapidly enough to promote diuresis in a few weeks. For these reasons the level of the serum albumin appears to be the critical factor in the formation of ascites, whereas portal hypertension appears to determine the site at which the transfer of fluid takes place.

Fiessinger (81) has emphasized that in addition to the increase in the portal blood pressure and the decrease in colloid osmotic pressure of the serum, a possible increase in the permeability of the mesenteric capillaries may play a role in the pathogenesis of ascites in cirrhosis. As far as could be ascertained, there are no definitive studies relative to this subject.

Edema

Almost as frequent in appearance as ascites, *edema*, usually of the lower extremities, was present in 61 per cent of the 386 patients in this study. It was noted before the appearance of ascites in 32 instances. Edema was observed in 16 patients in whom ascites was not described.

The frequent occurrence of edema in cirrhosis is generally recognized. Chapman, Snell and Rowntree (54, 55) found that edema was present in 20 of 58 patients who had cirrhosis without ascites, and in 83 of 112 patients with cirrhosis and ascites. In Henrikson's (115) series, 44 per cent of 162 patients with cirrhosis had edema.

The edema is usually of the lower extremities, but may occur elsewhere. Rao (212) noted that among 64 patients with portal cirrhosis who had ascites, 56 had edema of the feet, 5 had edema of the abdominal wall, and 4 had anasarca. Edema of the face in Laennec's cirrhosis is rare, although it has been described in a number of cases (35, 205, 88) in which renal disease was not discovered.

The appearance of edema before the recognition of ascites was described by Austin Flint (83) in 11 of 21 cases. Bartholow (16) observed, however, that "The ankles have in rather rare cases appeared swollen before the abdomen, but the detection of fluid in the peritoneal cavity when in small quantities is not always easy."

The level of the serum albumin appears to be of primary importance in the formation of edema in cirrhosis. In a parallel study of 54 cases (192), edema

occurred in 85 per cent of patients and in all instances it was associated with low serum albumin. Edema was not present in patients with normal serum albumin. With the accumulation of ascites, edema became increased in the legs, presumably because of pressure from ascites transmitted to the inferior vena cava and lymphatic trunks. The venous pressure in the femoral veins may be much increased when there is ascites. Conversely, peripheral edema generally diminishes after abdominal paracentesis. Myers and Keefer (180) and others have shown that the formation of edema and ascites may also be associated with low serum albumin in cases of acute hepatitis.

Numerous studies have been made on the urine output during 24 hour periods. A rhythmic function has been described (86) characterized by a "secretory phase" by day and an "assimilating phase" by night. It has been assumed by a number of workers that the liver regulates this rhythmic function, and that the abnormal retention of fluid in the presence of liver disease may be due in part to a disturbance of regulatory function. As yet this mechanism remains a mystery. Literature on this subject is cited by Jervell (128) and by Jones and Eaton (134). These authors likewise present evidence of abnormal water retention in cases of acute hepatitis and cirrhosis of the liver. Data on the serum proteins are not included in their reports. The lowering of serum albumin and thereby of osmotic pressure is ample explanation for water retention in most cases of cirrhosis of the liver. In certain instances, however, there are exceptions which suggest that other factors may be involved. Adequate studies on electrolyte pattern, hormonal activity and vessel permeability have not been made in this regard. Since many factors are involved in the exchanges of body fluids (197), it would be premature to ascribe a "regulatory" function to the liver until more substantial evidence is at hand.

Jaundice

Jaundice was described in 252, or 65 per cent of the patients in this series at one time or another during the course of the disease. Ordinarily mild in degree, it was occasionally severe. Thus 67 per cent of 143 determinations of the serum bilirubin were 1.0 mgm. per 100 cc. or higher, 40 per cent were 3.0 mgm. per 100 cc. or higher, and 20 per cent 4.0 mgm. per 100 cc. or higher. Of 199 determinations of the *icteric index*, 80 per cent were 10 units or higher, and 20 per cent were 50 units or higher, most values falling between 10 and 25 units. *Jaundice* was present for longer than three months in 112 patients, or 29 per cent of this series. In 102 patients, or 40 per cent of the 245 fatal cases, it did not appear until the last three months of life. The severity of the jaundice varied from time to time. At least 41 patients, or 16 per cent of those who were jaundiced, had definite complete remission although in many of these the icterus recurred.

Two hundred five patients had both jaundice and ascites. Twenty-one per cent of these patients were said to have had jaundice before the appearance of ascites. In 47 jaundiced patients ascites was not described at any time.

Icterus was present in half of 372 patients with cirrhosis reported by Ep-

pinger (73) Rolleston and McNee (227) collected 293 cases of cirrhosis from the British literature, in 36.5 per cent of which the patients were jaundiced. Icterus was present in 40 per cent of 431 patients studied at autopsy by Roch and Wohlers (221). Similar findings have been reported by others (101, 124).

The association of jaundice and ascites in cirrhosis was reviewed by Nissen (183). Among 77 patients in whom "alcoholic" cirrhosis was present at autopsy, there were 16 who had jaundice without ascites, 44 with both jaundice and ascites, and 17 who had ascites without jaundice.

The clinical significance of jaundice in patients with cirrhosis of the liver has not been popularly appreciated. The seriousness of this sign is indicated by an analysis of the duration of life after the onset of jaundice in 168 fatal cases (Figure 3). In brief, half of these patients died in less than 2 months and 85 per cent died within one year of the onset of jaundice. It is inferred that the presence of jaundice in patients with cirrhosis of the liver indicates activity of the disease process.

The pathogenesis of jaundice in cirrhosis is not clearly understood. The fragility of the red blood corpuscles to hypotonic saline is normal (140, 188, 78). Von Jaksch (283) and others (250, 47) noted that *urobilinuria* is frequently present in patients with Laennec's cirrhosis. However, it seems unlikely that the jaundice is of hemolytic origin.

In an attempt to correlate the presence of jaundice with the presence of necrosis of the parenchymal cells of the liver, the autopsy protocols of 77 patients with cirrhosis were analyzed. Table 16 lists the data in this study. It can be seen that in this group, only half of those patients with jaundice had necrosis of liver cells on histologic examination. In a group of 54 patients previously referred to (192), jaundice was present in 63 per cent. Autopsy study in 21 patients also showed no correlation between the presence of jaundice and necrosis of liver cells. The absence of necrosis, to be sure, does not exclude functional derangement.

Clay-colored stools were observed in 13 of the 386 patients in the present series, although there was no evidence of obstruction to the extra-hepatic biliary passages. This symptom was described in 8 of 162 patients with cirrhosis by Henrikson (115).

Jaundice is thus a common sign of cirrhosis of the liver, particularly during the terminal stages of the disease. The presence of jaundice, as shown by survivorship curves, carries an ominous prognostic significance, and it indicates activity of the disease process. It is stated by certain observers that the periodic appearance of jaundice in the course of cirrhosis implies superimposed acute degeneration (hepatitis). There is little or no evidence in the present study to support this point of view.

Liver and spleen

Two hundred ninety-one, or 75 per cent of the patients in this series, were said to have *palpable livers*. An attempt was made to correlate the weight of the liver as found at autopsy, with its palpability. The average weight of 78

palpable livers which showed cirrhosis was 1820 grams, the weights ranging from 695 to 5100 grams. On the other hand, 30 non-palpable livers with cirrhosis weighed an average of 1370 grams, ranging from 570 to 2920 grams. Table 17 lists the weights of these 108 livers. It demonstrates that there is only a rough correspondence between liver size and palpability. The average weight of the liver in these 108 patients with cirrhosis was 1690 grams.

There are many studies concerning the size of the liver in patients with cirrhosis. Eppinger (74) reported that in 80 per cent of patients the liver was enlarged to palpation, although on pathologic examination it was enlarged in only 50 per cent of cases. Foxwell (89) in 1896 pointed out that the liver might be palpable without being above average weight. Rolleston and Fenton (226)

TABLE 16

Jaundice and necrosis of parenchymal cells of the liver in 77 cases of Laennec's cirrhosis

	NECROSIS	NO NECROSIS
No jaundice	4 cases	16 cases
Jaundice for longer than 3 months	8	7
Jaundice for less than 3 months before death	22	20

TABLE 17

Weight of the liver in 108 cases of Laennec's cirrhosis

WEIGHT IN GRAMS	NUMBER WITH LIVER PALPABLE	NUMBER WITH LIVER NOT PALPABLE
200-999	8	6
1000-1399	18	13
1400-1799	17	7
1800-2199	15	2
2200-2599	11	0
2600-2999	3	2
3000-3799	3	0
3800-4599	2	0
4600-5400	1	0
Total	78	30

observed that the livers of patients with cirrhosis who were alcoholics weighed on the average more than those of non-alcoholics with cirrhosis. The correlation between the weight of the liver and the type of alcoholic beverage drunk is negative (226, 89).

Chapman, Snell and Rowntree (54, 55) observed that the liver was palpable in 48 of 58 patients who had cirrhosis without ascites, and in 69 of 112 patients with ascites. Evans and Gray (75) reported that of 211 livers which showed cirrhosis 100 weighed 1500 grams or more, and 111 weighed less than 1500 grams. Richard Bright is credited with having stated that during the course of cirrhosis, the liver was first enlarged and later diminished in size (39). As far as can be ascertained, there is no statistical evidence to support this opinion.

A firm, palpable spleen was present in 170 patients, or 44 per cent of this series.

The average weight of 43 palpable spleens was 580 grams, ranging from 180 to 1700 grams. Sixty-eight non-palpable spleens weighed an average of 320 grams, ranging from 30 to 940 grams. The average weight of the spleen in these 111 patients was 420 grams. Table 18 lists the weight of the spleen in patients with cirrhosis. It can be seen that a palpable spleen is much more likely to represent an enlarged spleen than a palpable liver is to represent an enlarged liver. In many patients, the presence of ascites must have prevented the palpation of an enlarged liver or spleen.

Enlargement of the spleen is frequent in patients with cirrhosis. Chapman, Snell and Rowntree (54, 55) reported that the spleen was palpable in 27 of 58 patients who had cirrhosis without ascites, and in 49 of 112 patients with ascites. Klopstock (141) found that the spleen was enlarged in 198 of 250 patients in whom cirrhosis was present at autopsy. Eppinger (74) observed that the spleen was clinically enlarged in 69 per cent of 372 patients with cirrhosis.

TABLE 18
Weight of the spleen in 111 cases of Laennec's cirrhosis

WEIGHT OF THE SPLEEN	NUMBER WITH SPLEEN CLINICALLY PALPABLE	NUMBER WITH SPLEEN NOT CLINICALLY PALPABLE
<i>grams</i>		
0-199	1	18
200-399	11	28
400-599	12	18
600-799	9	3
800-999	5	1
1000-1199	3	0
1200-1399	1	0
1400-1599	0	0
1600-1799	1	0

The palpability of the liver apparently depends not only on its size but on the density of the organ as well as the resistance of the abdomen to palpation. On this account there is a poor correlation between the palpability of the liver and its actual size. Although the liver was palpable in 75 per cent of the present series, the weight at autopsy was normal or subnormal in 63 per cent. However, enlargement of the spleen is common at autopsy whether or not this organ is palpable during life.

VASCULAR CHANGES OCCURRING IN PATIENTS WITH CIRRHOSIS OF THE LIVER

Collateral circulation

Dilated veins, evidence of collateral circulation between the portal and systemic circulations, appeared upon the abdomen and chest in 91, or 23.6 per cent of the patients in this series. In 4 patients, a large group of dilated veins, the "caput medusae", appeared around the umbilicus.

Chapman, Snell and Rowntree (54, 55) reported that of 58 patients who had cirrhosis without ascites, 7 had evidence of collateral circulation, whereas this

was present in 57 of 112 patients who had cirrhosis with ascites Jankelson and Baker (127) were able to demonstrate by means of infra-red photography enlarged tortuous collateral veins in the abdominal wall before they were visible to the naked eye

Numerous case reports have been published describing patients in whom the portal and systemic circulations were connected by means of large dilated collateral veins joining the umbilical or para-umbilical veins with the internal mammary veins In these cases, a palpable, continuous thrill and a continuous murmur may be present in the epigastrium. (270 155 310) Thayer (269) reviewed this subject in 1911, and described a patient in whom the thrill and murmur disappeared a few hours before death

Hemorrhoids were present in 105 of the 386 patients in this series In recent years it has been recognized that a large proportion of the population of the age group of patients with cirrhosis suffer from hemorrhoids As White (298) pointed out, it is questionable whether hemorrhoids occur more frequently among patients with cirrhosis than in other people In 4 of the patients in this series however the onset of hemorrhoids seemed definitely related to their illness Chapman, Snell and Rowntree (54, 55) found hemorrhoids in 9 of 58 patients who had cirrhosis without ascites, and in 46 of 112 patients with cirrhosis with ascites If these observations are correct, they suggest that hemorrhoids are the result not only of portal stasis but also of pressure exerted by the ascitic fluid upon the inferior vena cava or the hemorrhoidal veins

"Vascular spiders

An accurate analysis of the frequency of various skin lesions in patients with cirrhosis is not possible from the data available "*Spider angiomas*" were described in 15 per cent of the patients in this series, and *telangiectasia* in 17 per cent The association of the vascular "spider" with cirrhosis of the liver has been reviewed recently by Patek Post and Victor (193) They described the "spider" as a "bright red lesion characterized by a central point from which radiate fine hair-like branches for a distance of about 1 cm. usually occurring on the skin of the face, arms, fingers and upper trunk and only occasionally on the lower trunk and limbs It was possible to demonstrate pulsations in the spiders Histologic sections revealed that the spiders were of two types In one variety it appeared to be an artery branching into arterioles In the second group the junction between the afferent artery and the central vessel of the spider had the histologic appearance of a 'glomus, except that it branched into capillaries instead of forming arterio-venous anastomoses Forty-eight of 63 patients with cirrhosis were observed to have spiders In 3 patients, spurting hemorrhages from the spiders occurred

The spiders may appear long before the recognition of clinical symptoms of cirrhosis (214) Bloomfield (24) described a patient in whom large spider angiomas disappeared with the remission of the symptoms of cirrhosis

Williams and Snell (302) have recently reviewed the association of large pulsating angiomas and cirrhosis They pointed out that cirrhosis may com-

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WEIGHT OF THE SPLEEN	NUMBER WITH SPLEEN CLINICALLY PALPABLE	NUMBER WITH SPLEEN NOT CLINICALLY PALPABLE
<i>grams</i>		
0-199	1	18
200-399	11	28
400-599	12	18
600-799	9	3
800-999	5	1
1000-1199	3	0
1200-1399	1	0
1400-1599	0	0
1600-1799	1	0

The palpability of the liver apparently depends not only on its size but on the density of the organ as well as the resistance of the abdomen to palpation. On this account there is a poor correlation between the palpability of the liver and its actual size. Although the liver was palpable in 75 per cent of the present series, the weight at autopsy was normal or subnormal in 63 per cent. However, enlargement of the spleen is common at autopsy whether or not this organ is palpable during life.

VASCULAR CHANGES OCCURRING IN PATIENTS WITH CIRRHOSIS OF THE LIVER

Collateral circulation

Dilated veins, evidence of collateral circulation between the portal and systemic circulations, appeared upon the abdomen and chest in 91, or 23.6 per cent of the patients in this series. In 4 patients, a large group of dilated veins, the "*caput medusae*", appeared around the umbilicus.

Chapman, Snell and Rowntree (54, 55) reported that of 58 patients who had cirrhosis without ascites, 7 had evidence of collateral circulation, whereas this

was present in 57 of 112 patients who had cirrhosis with ascites. Jankelson and Baker (127) were able to demonstrate by means of infra-red photography enlarged tortuous collateral veins in the abdominal wall before they were visible to the naked eye.

Numerous case reports have been published describing patients in whom the portal and systemic circulations were connected by means of large dilated collateral veins joining the umbilical or para-umbilical veins with the internal mammary veins. In these cases a palpable continuous thrill and a continuous murmur may be present in the epigastrium. (270 155 310) Thayer (269) reviewed this subject in 1911 and described a patient in whom the thrill and murmur disappeared a few hours before death.

Hemorrhoids were present in 105 of the 386 patients in this series. In recent years it has been recognized that a large proportion of the population of the age group of patients with cirrhosis suffer from hemorrhoids. As White (298) pointed out it is questionable whether hemorrhoids occur more frequently among patients with cirrhosis than in other people. In 4 of the patients in this series however, the onset of hemorrhoids seemed definitely related to their illness. Chapman, Snell and Rowntree (54 55) found hemorrhoids in 9 of 58 patients who had cirrhosis without ascites, and in 46 of 112 patients with cirrhosis with ascites. If these observations are correct, they suggest that hemorrhoids are the result not only of portal stasis but also of pressure exerted by the ascitic fluid upon the inferior vena cava or the hemorrhoidal veins.

"Vascular spiders"

An accurate analysis of the frequency of various skin lesions in patients with cirrhosis is not possible from the data available. '*Spider angiomas*' were described in 15 per cent of the patients in this series and *telangiectasia* in 17 per cent. The association of the vascular "spider" with cirrhosis of the liver has been reviewed recently by Patek, Post and Victor (193). They described the 'spider' as a "bright red lesion characterized by a central point from which radiate fine hair-like branches for a distance of about 1 cm. usually occurring on the skin of the face, arms, fingers and upper trunk, and only occasionally on the lower trunk and limbs. It was possible to demonstrate pulsations in the spiders. Histologic sections revealed that the spiders were of two types. In one variety it appeared to be an artery branching into arterioles. In the second group the junction between the afferent artery and the central vessel of the spider had the histologic appearance of a "glomus, except that it branched into capillaries instead of forming arterio-venous anastomoses. Forty-eight of 63 patients with cirrhosis were observed to have spiders. In 3 patients spurting hemorrhages from the spiders occurred.

The spiders may appear long before the recognition of clinical symptoms of cirrhosis (214). Bloomfield (24) described a patient in whom large spider angiomas disappeared with the remission of the symptoms of cirrhosis.

Williams and Snell (302) have recently reviewed the association of large pulsating angiomas and cirrhosis. They pointed out that cirrhosis may com-

plicate hereditary hemorrhagic telangiectasis (Osler-Rendu-Weber syndrome) Weber (289) and Van Bogaert (279) have described familial instances of this syndrome

"*Liver palms*," a condition in which the thenar and hypothenar eminences are pink and flushed, were described in 16 of the 386 patients in this series. It is the authors' impression that these occur more commonly than the figures suggest. It may be pointed out that similar changes are observed in other conditions, notably rheumatoid arthritis. The nature of these changes is unknown.

Cardio-respiratory signs

Cyanosis was observed in 19 patients, or 5 per cent of the series. Of the 19 patients with cyanosis, 3 had clubbed fingers, and 8 were dyspneic. None of the patients had hydrothorax. Fifteen patients were noted to be cyanosed either at the same time or after the appearance of ascites. In 2 of the patients who were cyanosed, ascites was not described. In 2 others, the cyanosis was said to precede the onset of ascites.

Cyanosis was described in 23 of 162 patients with cirrhosis reported by Henrikson (115). Keys and Snell (139) observed that the oxygen saturation of the arterial blood was subnormal in 8 of 14 patients with cirrhosis. They suggested that in cirrhosis there might be an alteration in the affinity between oxygen and hemoglobin. Darling (64) found the mean oxygen saturation of the arterial blood of 34 patients with cirrhosis was 95.0 per cent, only 0.5 per cent below normal. Subnormal values of arterial oxygen saturation were observed in 9 instances. In 3 of these there was co-existing pulmonary disease.

Bouchut, Froment and Grasset (34) correlated the clinical and pathologic evidence of cardio-vascular disease in 160 patients observed to have "alcoholic" cirrhosis at autopsy. In 65 per cent of the cases the systolic blood pressure was normal, in 10 per cent it was less than 110 mm Hg, and in 25 per cent, more than 140 mm Hg. The weight of the heart was not significantly abnormal in 80 per cent of cases. The remaining 31 hearts weighed more than 400 grams. In 18 instances the hypertrophy could be explained on the basis of obvious cardio-vascular pathology, such as syphilis, hypertension, chronic nephritis or myocarditis. It seems reasonable to conclude that the cardio-vascular status of patients with cirrhosis of the liver does not differ materially from that of patients of a comparable age group.

Chauffard and Routier (56) believed that arrhythmias, especially extrasystoles, were frequent in Laennec's cirrhosis. The data in the present series do not support this belief. Moreover, arrhythmias were present in only 2 of Bouchut's 160 cases (34).

Excluding those patients who had chronic pulmonary disease, 16 of the 386 patients in this series were described as having *clubbed fingers* and 5 others were said to have excessive curving of the finger nails. Seventeen of these 21 patients had ascites, and 5 had hydrothorax. Three of the patients were cyanosed, and 5 had dyspnea.

Clubbed fingers have been reported infrequently in patients with cirrhosis (67, 306, 72, 108) Darling (64) observed clubbed fingers in 2 of 34 patients who had cirrhosis. One of these was a patient in whom the oxygen saturation of the arterial blood was less than 92 per cent. In the other patient, the oxygen saturation of the arterial blood was 96.5 per cent, a normal value.

Hydrothorax

Hydrothorax is not unusual in Laennec's cirrhosis. In 25 of the 386 patients, hydrothorax was discovered by physical examination, roentgenographic examination, or at autopsy. In 9 of these, the hydrothorax was limited to the right side of the chest, in 3 cases to the left side. It was bilateral in 8 instances. In 5 other cases the side on which the hydrothorax occurred was not specified. In 6 instances specific gravity determinations were made on the chest fluid. Of these, one was 1.010, three were 1.012, one was 1.013, and one was 1.014.

In 24 of the 25 patients with hydrothorax, ascites was also present. Five of the patients with hydrothorax had clubbed fingers or excessive curvature of the finger nails. None was cyanosed.

Hydrothorax was present in 19 of 54 cases of cirrhosis reported by Wang (287), and in 34 of 157 cases examined *post-mortem* by Barrera (13). Vedel and Puesch (280) reviewed the co-incidence of pleural effusion and cirrhosis of the liver. They reported that pleural effusion occurred in one-sixth to one-seventh of cases with Laennec's cirrhosis. The pleural fluid usually appears in conjunction with ascites and is usually accompanied by fever. Vedel and Puesch observed pleural effusion in the right and left pleural cavities with equal frequency. Blood is usually present in the pleural fluid on microscopic examination, and in three of their cases the fluid was grossly bloody. They attributed the presence of blood in the pleural fluid to the general hemorrhagic tendency of patients with cirrhosis. Vedel and Puesch believed that pleural effusions in cirrhosis might be the result of independent pathology such as nephritis or tuberculosis. Rarely, there was a hydrothorax for which no apparent cause was found. In most instances, however, the characteristics of the pleural fluid suggested that some inflammation was present. They believed that this might be the result of perihepatitis or perisplenitis adjacent to the diaphragm. Goffart (96) studied the pathogenesis of the pleural effusion in 10 patients with cirrhosis. He too observed that the pleural fluid was usually hemorrhagic. The protein content of the fluid never exceeded 3.7 grams per 100 cc. He believed that the hydrothorax resulted from a combination of factors. He thought mechanical stasis in the pulmonary vascular bed as the result of a high diaphragm due to ascites probably plays a role, but only inconstantly. Diminution of the colloid osmotic pressure of the blood was present in 6 of 8 patients with cirrhosis who had pleural effusion, as measured by a diminution in the serum albumin to 3.3 grams per 100 cc or less. Goffart believed it likely that an increase in capillary permeability was also present, although he did not study this factor. Tuberculosis was not present in any of Goffart's cases, and guinea-pig inoculation of the pleural fluid in 8 patients was negative.

Taylor (266) described a case of hemorrhagic pleural effusion in a 13-year old girl who was found at autopsy to have "multilobular" cirrhosis and 3 small infarcts in the posterior lobe of the lung Christian (58) reported a case of cirrhosis in which autopsy revealed no apparent cause for a hemorrhagic effusion in the pleural cavity Very rarely, hydrothorax may be the result of a traumatic perforation of the diaphragm permitting ascitic fluid to enter the thorax (99)

Hydropericardium

There were no instances of hydropericardium in this series Most authors likewise do not report its occurrence Barrera (13), however, noted that among 157 patients observed to have portal cirrhosis at necropsy in Manila, 11 patients, or 7 per cent, had hydropericardium Individual instances of pericardial effusion in cirrhosis have been reported by others (265, 34, 147) The amount or composition of the pericardial fluid was not stated

Neurological manifestations

Neurological examinations were made in 300 of the 386 patients in this series One hundred ninety-six, or approximately two-thirds of those examined, were found to have no abnormal neurological signs Forty patients, or about 13 per cent, had either the symptoms of *peripheral neuritis* or *absent deep reflexes*

The frequent occurrence of peripheral neuritis in patients with cirrhosis has only recently been recognized Roger, Cornil and Paillas (222) reported that 20 of 104 patients with cirrhosis had neurological signs characteristic of "alcoholic" peripheral neuritis paraplegia, dropped foot, absent deep reflexes, hypesthesia of the skin and hyperalgesia of the muscles and nerve trunks Women were affected three times as frequently as men Similar findings have been reported by others (191, 192, 288)

Wilson (304) made a careful study of a syndrome of bilateral symmetrical softening of the lenticular nucleus, especially the putamen, combined with a "multilobular or mixed" hepatic cirrhosis The disease may be familial and it usually occurs in children or young adults There are symptoms of corpus striatum disease, usually without any clinical evidence of hepatic disease A Kayser-Fleischer ring, a greenish ring at the outer margin of the cornea, is occasionally present (12) At times, (12, 208), clinical symptoms of cirrhosis may precede the appearance of neurological symptoms in *Wilson's disease* The etiology of Wilson's disease and its relation, if any, to Laennec's cirrhosis are unknown (Cf ref 315 for review of literature)

Mental changes, which are comparatively common in patients with Laennec's cirrhosis, were described in 28 of 386 patients in this series A "toxic delirium" was observed in 7 patients, "mania" in 3, and "delirium tremens" in 3 others Occasionally, Korsakow's psychosis, hallucinations, or delusions were said to be present

French (90) described a "noisy delirium" followed by coma as a terminal event in cirrhosis Thierfelder (270) observed that somnolence, delirium, convulsions and coma were common toward the end of the course of cirrhosis, and

emphasized that icterus need not be present. DeBenedetti (68) described patients with cirrhosis as characteristically *euphoric*. *Delirium tremens* was present in 5 per cent of 372 patients with cirrhosis studied by Eppinger (74). Portis (201) believes that depression, headache, loss of memory, delirium, confusion, and coma are not uncommon in cirrhosis.

Recent studies indicate that certain of these mental changes, like the polyneuritis, may be related to co-existing nutritional deficiency. Snell (249) described encephalopathic states "similar to acute alcoholism and acute pellagra" in liver disease—mental confusion progressing to deep stupor and muscular spasticity and evidence of cerebral irritation. Three patients responded to therapy with large doses of nicotinic acid and thiamin chloride intravenously. Patek and Post (192) observed mental changes in one-third of their series of patients. These changes were characterized in certain patients by confusion and euphoria and in others by torpor simulating "cholemia". In addition, lateral nystagmus was observed in 10 patients. These changes (except for nystagmus) cleared with dietary therapy.

It is therefore likely that certain of the nervous manifestations of cirrhosis are due to co-existing nutritional deficiency rather than to "cholemia". The experimental production of encephalitis by dietary deficiency (4) might support this point of view.

Fever

Excluding all cases in which a patent cause such as secondary infection or hemorrhage, was present, there were 93 patients or 24 per cent of those with cirrhosis who had a temperature of 100°F or more while under observation. The fever was usually protracted and of low grade. Five patients had a spiking temperature reaching 102°F each day. Chills and fever with temperatures as high as 103°F were noted in 13 patients in 11 of whom pathologic examination was made.

The frequent occurrence of fever in Laennec's cirrhosis is not often appreciated. Eppinger (74) noted that fever was present without apparent cause in 20 per cent of patients with cirrhosis. Carrington (49) reviewed the charts of 50 patients who were thought to have uncomplicated cirrhosis, and noted that 18 patients were febrile. In 81 patients with uncomplicated portal cirrhosis King (140) found that 14 were afebrile, 56 had temperatures between 99° and 101°F, 4 had temperatures between 101°F and 103°F, and 7 patients had temperatures between 103° and 105°F.

Concurrent blood disorders

In this series there were 2 patients with Addisonian pernicious anemia, confirmed at autopsy; one patient with sickle-cell anemia, and one with polycythemia vera which had been treated with phenylhydrazine.

There have been occasional case reports on the coincidence of cirrhosis of the liver and Addisonian pernicious anemia. Remen (213), in 1932 reviewed the literature collecting 5 cases proved pathologically, in addition to his own

McCartney (165) observed one instance of pernicious anemia among 245 cases of cirrhosis at autopsy, and Wintrobe and Schumacker (307) reported 2 cases among 138 autopsies on patients with cirrhosis. Bigg (23) noted that of 200 patients with pernicious anemia, 6 had palpable spleens, one of these 6 patients was found to have cirrhosis at *post-mortem*. Since malnutrition, gastritis, and achlorhydria occur frequently in patients with cirrhosis of the liver, the coincidence of pernicious anemia might be anticipated.

As well as could be ascertained, there are no reports concerning the coincidence of sickle-cell anemia and cirrhosis. Bauer (17), however, has described pathologic changes in the liver of patients with sickle-cell anemia. The liver cells may show vacuolization, fatty change and necrosis. There may be proliferation of the Kupfer cells, perivascular infiltration with lymphocytes and monocytes, and some periportal fibrosis.

A review of the literature indicates that cirrhosis of the liver occasionally complicates polycythemia vera. Harrop (113) found that in at least half of the clinical reports of polycythemia vera there was enlargement of the liver. He believed that cirrhosis is a rather common terminal event in polycythemia. Sohval (252) collected 10 cases from the literature in which polycythemia was complicated by cirrhosis. Phenylhydrazine had been used to treat 3 of the patients and Sohval pointed out that this drug can produce cirrhosis experimentally. Hurst and Hurst (122), however, found that phenylhydrazine only rarely produced cirrhosis in guinea-pigs.

It has long been known that anemia is frequently present in cirrhosis (16). Holler and Kudelka (117) showed that in 3 of 5 patients with cirrhosis, the mean corpuscular diameter of the red blood corpuscles was increased. Wintrobe (308) studied the blood picture in 23 patients who had Laennec's or "toxic" cirrhosis. Anemia was present in every instance. In 10 cases the anemia was macrocytic, in 11 it was normocytic, and in 4 others, hypochromic microcytic in type. The cause of macrocytic anemia in cirrhosis is not clear. Wintrobe and others (308, 97, 95) have reported a reticulocyte response following therapy with liver extract in patients who have cirrhosis with macrocytic anemia. It has been suggested that the macrocytic anemia of cirrhosis is caused by failure of the liver to store the specific anti-anemic substance of pernicious anemia. The demonstration by Schiff and his co-workers (232) that this substance is present in human livers with cirrhosis renders such an hypothesis untenable.

There is considerable variation in the leukocyte count in patients with cirrhosis. Rolleston and McNee (227) believed that *leukocytosis* did not occur in patients with cirrhosis in the absence of complications. *Leukopenia* was described in 36 per cent of patients studied by Eppinger (74). King (140) analyzed the white blood cell count of 61 patients with uncomplicated cirrhosis. The leukocyte count was less than 6,000 in 31 per cent of the cases, between 6,000 and 10,000 in 41 per cent of the cases, and between 10,000 and 15,000 in 28 per cent of the cases. Seven of the 17 patients with leukocytosis had temperatures ranging from 101° to 105°F. In most instances there was a normal leukocyte response to infection. The leukocyte count tends to be lower in those patients in whom extreme splenomegaly is present.

COMPLICATIONS

Intercurrent infection

Laennec's cirrhosis is frequently complicated and often terminated by secondary infection. Table 19 lists some of the intercurrent infections that may occur in patients with cirrhosis. *Peritonitis* was observed in 12 of the 386 patients in this series. *Erysipelas* infection about a paracentesis wound, and *phlebitis* occurred in a few cases. *Tuberculosis* was present clinically in only four patients, of whom 2 had tuberculous peritonitis. Of 150 patients studied at autopsy, only 3 were found to have active tuberculosis. One patient had parotitis.

Blumenau (26) reported that of 126 patients observed to have cirrhosis at autopsy, 10 per cent died of tuberculosis, and 26 per cent of such other infections as pneumonia, peritonitis, and erysipelas. McCartney (165) studied at autopsy 158 patients who died of cirrhosis, and noted that there were 5 patients who had pneumonia, 12 who had peritonitis, 2, tuberculous peritonitis, one,iliary

TABLE 19

Intercurrent infection during the course of Laennec's cirrhosis in 586 patients

INFECTION	NUMBER OF CASES
Bronchopneumonia	17
Non-tuberculous peritonitis	12
Lobar pneumonia	5
Bacteremia	4
Erysipelas	3
Phlebitis	3
Tuberculous peritonitis	2
Chronic pyelonephritis	2

Also 1 each—tuberculous peritonitis, tuberculosis site unspecified, bacterial meningitis, infected (bacterial) paracentesis wound, parotitis, "acute inflammation of the eye," bacterial mastoiditis, cystitis.

tuberculosis, 2, pulmonary abscess 2, sepsis, and 1, erysipelas. Robert (220) noted that 6.7 per cent of patients who had Laennec's cirrhosis at autopsy had coincidental acute *endocarditis*, compared with 3.4 per cent of a control series. Four of his patients died of *pachymeningitis*, and 3 of sepsis. A number of cases have been reported (284) in which the patient died of *staphylococcus sepsis*. Three of Cheadle's (57) 53 patients with cirrhosis had facial erysipelas.

Since intercurrent infections are an important cause of death in patients with cirrhosis of the liver, the control of such infections should influence favorably the prognosis of this disease. The present series of cases preceded the introduction of sulfonamide drugs for the treatment of infections. However, in our personal experience, 17 patients have been treated with sulfonamide drugs for pneumonia, facial and wound erysipelas, and phlebitis. With possibly two exceptions this therapy was effective and well tolerated. In the authors' opinion, the presence of cirrhosis of the liver does not contraindicate the judicious trial of these drugs.

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Seventeen of the 386 patients in this series were said to have developed *umbilical herniae* during the course of their illness. Three of these herniae became incarcerated, with fatal results in two instances. In one patient, the appearance of an inguinal hernia was the first symptom of cirrhosis. On the basis of incomplete data, 13 additional patients had inguinal herniae.

Blumenau (26) reported that of 128 patients in whom cirrhosis was discovered at autopsy, 3 had died as the result of incarceration of herniae. Chapman, Dell and Rowntree (54, 55) noted that of 58 patients who had cirrhosis without ascites, 6 had herniae, but of 112 patients in whom ascites was present, 47 had herniae. These herniae were umbilical in 24, ventral in 7, inguinal in 9, and epigastric in 2 instances. In 5 patients the location of the herniae was not designated. Altschule (5) has recently emphasized the frequent occurrence of herniae in patients with cirrhosis. He described 4 patients in whom herniae were very early symptoms of the disease. The increased intra-abdominal pressure resulting from the presence of ascites seems to precipitate the appearance of herniae.

Coincidence of peptic ulcer

Fourteen patients, or 3.6 per cent of this series, had a history of peptic ulcer concurrent with, or preceding their present illness.

Although descriptions of cirrhosis seldom mention the occurrence of peptic ulcer, the two diseases have been reported as coincident in a rather high proportion of instances. Schnitker and Hass (236) found that among 72 cases of advanced cirrhosis studied at autopsy 14, or 19.5 per cent, had peptic ulcers. Conversely, of 100 patients with gastric or duodenal ulcers, 14 had cirrhosis. Skanazy (7) reported that of 64 patients with various types of cirrhosis at autopsy, 5 had gastric ulcers. In Japan, Suzuki (261) noted that among 21 cases of Laennec's cirrhosis at necropsy, there were 3 patients with peptic ulcer. In 38 instances of hepatic cirrhosis studied *post-mortem* Ask-Upmark (8) observed 9 instances of peptic ulcer, 7 of which were in an active stage. Rabl (207) reported that peptic ulcer was present in patients with cirrhosis in 9 per cent of cases in Leipzig, but in only 1.8 per cent of cases in Russia. It seems probable, therefore, that peptic ulcer is an occasional concomitant of Laennec's cirrhosis. The reason for this association is not clear.

Portal vein thrombosis

Occasionally, *thrombosis of the portal vein* may complicate Laennec's cirrhosis. Engdon Brown (37) reviewed the early literature, and reported that portal vein thrombosis occurred in 3 per cent of 334 patients in whom cirrhosis was present at autopsy. Weir and Beaver (294) reported eight instances of portal cirrhosis or "chronic toxic yellow atrophy" which were complicated by either intra- or extra-hepatic portal thrombosis. With one exception, all these patients had ascites. Osler (189) observed that rapidly developing ascites followed the formation of a portal vein thrombus, due presumably to the sudden increase in

portal pressure. However, it should be pointed out that the rapid onset of ascites may occur without portal vein thrombosis and that portal vein thrombosis also may occur without the rapid onset of ascites.

Renal disease

In recent years there has been much discussion concerning the renal complications of liver disease. Twenty-five of the patients in this series or 6.5 per cent were said to have chronic nephritis or hypertensive cardio-vascular-renal disease, and 2 patients had chronic pyelonephritis. Albuminuria was present in 46 of the 386 patients with cirrhosis in this series. Albuminuria is not uncommon in Laennec's cirrhosis, although the frequency with which it is reported to occur varies widely from clinic to clinic. Rolleston and McNee (227) thought albuminuria rare while Henrikson (115) found it in 47 per cent of 151 cases of cirrhosis. Murchison (179) and much later Rao (212) thought that albuminuria disappeared following paracentesis. This would suggest that the albuminuria was the result of renal stasis caused by pressure on the renal vein from the ascitic fluid.

There is disagreement in the literature concerning the frequency of renal complications in Laennec's cirrhosis (227, 207, 223). Whether or not there is an increased incidence of renal disease among patients with cirrhosis cannot be deduced from the data available. Apparently albuminuria occasionally occurs but there is no evidence that this is the result of anything more than congestion of the kidney resulting from the pressure of the ascitic fluid on the renal vein.

Gall-bladder disease

Cholecystitis and cholelithiasis are occasional complications of Laennec's cirrhosis although no apparent obstruction of the biliary ducts is present. Three per cent of the patients in this series had cholecystitis. Unfortunately there are no data concerning the frequency of cholelithiasis.

Rabl (207) compared the incidence of cholelithiasis at autopsy in patients with cirrhosis and those without cirrhosis. The incidence of cholelithiasis in patients with cirrhosis varied from 3.0 per cent in the Transcaucasus to 19.2 per cent in Leipzig, but it was invariably much higher in patients with cirrhosis than in the controls.

PROGNOSIS

Two hundred forty-five of 386 patients in this series were followed until their death. More than 60 per cent of these fatal cases had died within one year of the first symptoms of the disease. An additional 117 were lost to follow-up at one or another stage of the illness. In many instances these patients left the hospital in a moribund condition. Only 24 patients in the series were known to be alive at the time the records were reviewed.

Ideally the prognosis of a disease should be determined by tracing the course of a large complete series from first symptoms until death. In the case of cirrhosis of the liver this is impossible because these patients are comprised

Herniae

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Coincidence of peptic ulcer

Fourteen patients, or 3.6 per cent of this series, had a history of peptic ulcer concurrent with, or preceding their present illness.

Although descriptions of cirrhosis seldom mention the occurrence of peptic ulcer, the two diseases have been reported as coincident in a rather high proportion of instances. Schnitker and Hass (236) found that among 72 cases of advanced cirrhosis studied at autopsy, 14, or 19.5 per cent, had peptic ulcers. Conversely, of 100 patients with gastric or duodenal ulcers, 14 had cirrhosis. Askanazy (7) reported that of 64 patients with various types of cirrhosis at autopsy, 5 had gastric ulcers. In Japan, Suzuki (261) noted that among 21 cases of Laennec's cirrhosis at necropsy, there were 3 patients with peptic ulcer. In 38 instances of hepatic cirrhosis studied *post-mortem* Ask-Upmark (8) observed 9 instances of peptic ulcer, 7 of which were in an active stage. Rabl (207) reported that peptic ulcer was present in patients with cirrhosis in 9 per cent of cases in Leipzig, but in only 1.8 per cent of cases in Russia.

It seems probable, therefore, that peptic ulcer is an occasional concomitant of Laennec's cirrhosis. The reason for this association is not clear.

Portal vein thrombosis

Occasionally, *thrombosis of the portal vein* may complicate Laennec's cirrhosis. Langdon Brown (37) reviewed the early literature, and reported that portal vein thrombosis occurred in 3 per cent of 334 patients in whom cirrhosis was present at autopsy. Weir and Beaver (294) reported eight instances of portal cirrhosis or "chronic toxic yellow atrophy" which were complicated by either intra- or extra-hepatic portal thrombosis. With one exception, all these patients had ascites. Osler (189) observed that rapidly developing ascites followed the formation of a portal vein thrombus, due presumably to the sudden increase in

SURVIVAL AFTER ONSET OF ASCITES

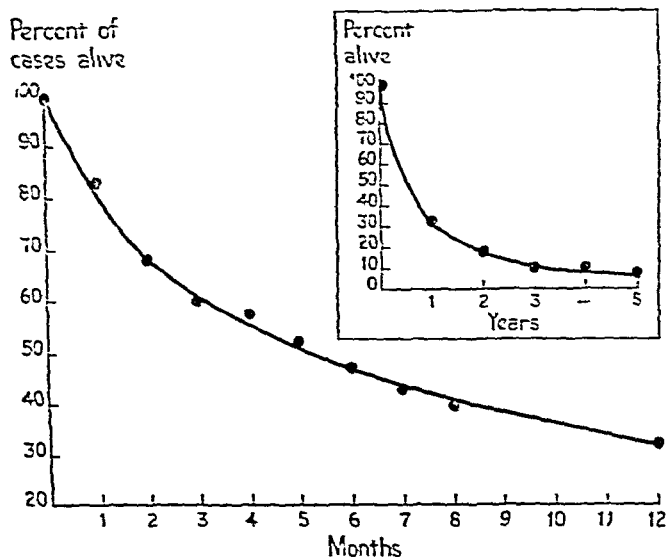


FIG 2 SURVIVAL AFTER THE ONSET OF ASCITES IN 296 PATIENTS WITH LAENNEC'S CIRRHOSIS

SURVIVAL AFTER ONSET OF JAUNDICE

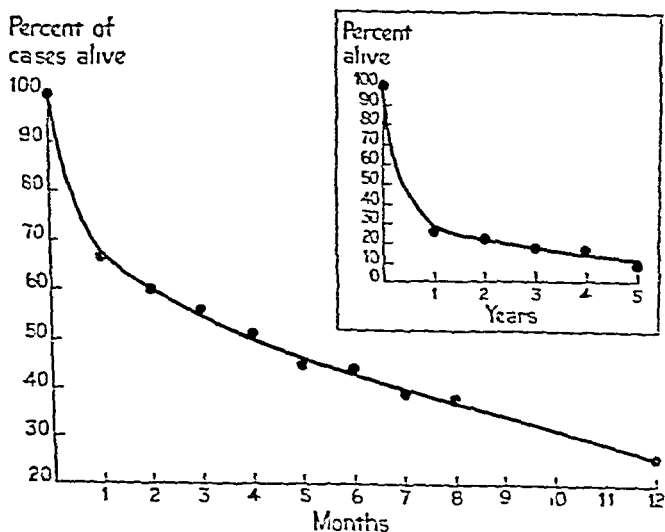


FIG 3 SURVIVAL AFTER THE ONSET OF JAUNDICE IN 245 PATIENTS WITH LAENNEC'S CIRRHOSIS

largely of alcoholics, who are a shiftless population. Moreover, the first symptoms of Laennec's cirrhosis may be vague and ill-defined, so that the patient's history is of questionable reliability, particularly when he is mentally dulled by his disease. For these reasons, the data are analyzed with respect to certain specific signs, i.e., ascites, jaundice, and hematemesis, which permit fairly accurate recognition by the patient. Survivorship tables were constructed according to standard methods employed in actuarial tables,³ and the computations include both living and dead patients.

Table 20 illustrates the method of computing survivorship of 296 patients after the onset of ascites. Figure 2 is a graphic presentation of these data. This figure reveals that after the onset of ascites, 47 per cent survived 6 months,

TABLE 20
Survival of patients with cirrhosis of the liver from onset of ascites

PERIOD	NUMBER OBSERVED AT BEGINNING OF PERIOD	DIED DURING THE PERIOD	DROPPED FROM OBSERVATION DURING THE PERIOD	PROPORTION DYING DURING THE PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD (q)	PROPORTION LIVING AT END OF PERIOD OF THOSE OBSERVED AT BEGINNING OF PERIOD (p = 1 - q)	PROPORTION SURVIVING AT END OF PERIOD OF ORIGINAL COHORT (1)
	A	B	C	D	E	F
1st month	296	50	16	0.169	0.831	0.831
2nd month	230	41	15	0.178	0.822	0.653
3rd month	174	21	12	0.121	0.879	0.600
4th month	141	8	8	0.057	0.943	0.566
5th month	125	10	4	0.080	0.920	0.521
6th month	111	10	7	0.090	0.910	0.474
7th month	94	9	2	0.096	0.904	0.428
8th month	83	6	2	0.072	0.928	0.397
9-12 months	75	14	15	0.187	0.813	0.323
2nd year	46	21	4	0.457	0.543	0.175
3rd year	21	8	1	0.381	0.619	0.108
4th year	12				1.000	0.108
5th year	12	4		0.333	0.667	0.072

32 per cent survived one year and but 17 per cent survived 2 years. The onset of ascites, thus, bears with it an ominous prognostic significance.

Similar computations were made for 245 patients following the onset of jaundice. (This refers to jaundice in the present illness and not to jaundice that antedated clinical evidence of cirrhosis.) The survivorship curve of these cases (Figure 3) is similar to that following the onset of ascites. This implies that the prognosis becomes grave after the onset of jaundice in patients with Laennec's cirrhosis. In the present series 44 per cent lived 6 months, 26 per cent lived one year, and 23 per cent lived two years after the onset of jaundice.

In the case of hematemesis the data are less satisfactory because of the smaller series of 106 patients in this group. Figure 4 reveals the period of survival.

³ The authors are indebted to Mr. Herbert Marks of the Metropolitan Life Insurance Company for his helpful criticism and technical assistance in the analysis of these data.

patients In his analysis of 372 cases Eppinger (73) gave no data on prognosis, but he stated that once abdominal paracentesis was performed a fatal outcome was imminent Bloomfield (24) reported that of 20 fatal cases of Laennec's cirrhosis, 40 per cent died within 6 months There are likewise numerous case reports (194, 54, 24, 276) of spontaneous recoveries in which patients lived years after the disappearance of ascites Although such instances are of interest, they are of limited value from a statistical point of view In the present series 7 per cent had spontaneous diuresis with the loss of ascites

In general the medical literature clearly reveals that the outlook is grave in Laennec's cirrhosis, particularly after ascites appears However, in most instances the data have not been adequate for a fair estimate of prognosis in this disease Usually the series have been too small for refined analysis, and usually prognosis has been expressed in terms of "average duration of life" It is obvious that in a small series of cases the "average duration" may be influenced greatly by a few cases at either extreme from the mode Likewise a bias is introduced if prognosis is determined from an analysis of fatal cases alone since this excludes the possibility of recovery in milder cases For these reasons, the authors believe that the present analysis affords a more accurate picture of the prognosis in Laennec's cirrhosis

CAUSE OF DEATH

The causes of death in 213 patients dying of Laennec's cirrhosis are listed in Table 21 Thirty-five per cent of these patients were said to have died of *liver failure or cholemia* This is an ill-defined state in which the symptoms of cirrhosis become intensified The patient may become stuporous or delirious, finally sinking into coma Jaundice is usually, but not invariably present

Hematemesis was the terminal episode in one-fourth of the patients in whom the cause of death was recorded Rarely death followed hematemesis in a patient apparently in good health Occasionally hematemesis complicated and hastened death from cholemia

Another one-fourth of the patients died of *secondary infections* In 22 of 213 instances, there was a complicating pneumonia and in 12, non-tuberculous peritonitis Only 4 patients in this series died of tuberculosis

Eppinger (74) analyzed the cause of death in 135 patients who had cirrhosis Sixteen per cent were said to have died of gastro-intestinal hemorrhages 16 per cent of "heart failure, 16 per cent in "coma" and 10 per cent of tuberculosis Thirty-seven per cent of 217 patients studied at autopsy by Evans and Gray (75) died of lobar or lobular pneumonia, 20 per cent of gastro-intestinal hemorrhage, and 12 per cent of "liver insufficiency" Five of the patients in the latter series were found to have thrombosis of the portal vein

There were 34 *post-operative* deaths in the present series This represents an operative mortality of 40 per cent In 30 operations in which the only procedure was omentopexy, there were 12 deaths within a short post-operative period

White (297) summarized the early literature dealing with the operative therapy of cirrhosis, and found that 33 per cent of the 227 patients upon whom omento-

after the first hematemesis in these patients. Forty per cent died within one month of this episode. Indeed, most of these patients died within a week of the initial hematemesis. An additional 30 per cent died by the end of the first year. Thereafter the slope of the curve is almost flat, indicating that if the patient survives one year after hematemesis there is a good chance of his surviving 2, 3, or 4 years. Clinical observations bear this out. There would seem to be a group of patients who died from hematemesis when other signs of liver failure are prominent, such as jaundice, ascites, and torpor. In this group, the episode hematemesis appears suddenly as a coup de grâce among these other signs of impending failure. These patients largely comprise the 40 per cent who die shortly after the first hematemesis. However, there remains a second group

SURVIVAL AFTER FIRST HEMATEMESIS

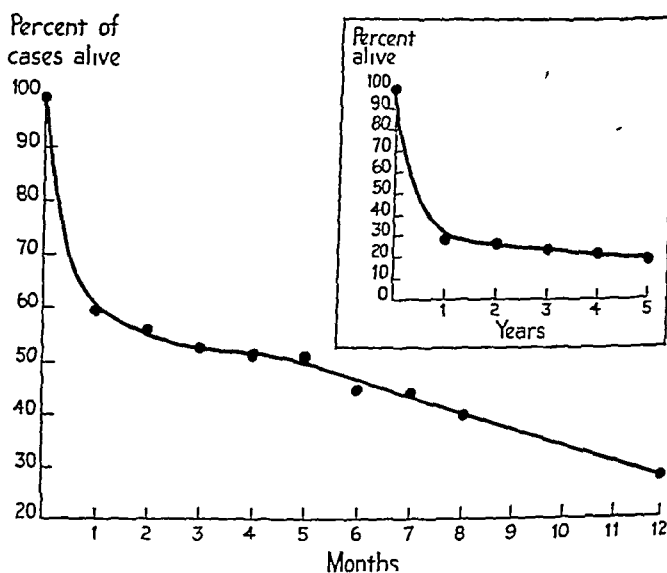


FIG 4 SURVIVAL AFTER THE FIRST HEMATEMESIS IN 106 PATIENTS WITH LAENNEC'S CIRRHOSIS

of patients who in other respects are vigorous and in whom Laennec's cirrhosis is latent and unsuspected until hematemesis occurs. For such patients the hematemesis is a "vascular accident" which usually is survived if transfusions are promptly given. In this latter group, hematemesis does not appear to reflect a failure of liver parenchyma, but rather a selective weakness in the vascular structure.

In earlier reports, cited by Patterson (194) and by Chapman, Snell and Rowntree (54) the average life expectancy after the onset of ascites varied from 1 to 6 months. In a series of 38 cases Rolleston and McNee (227) reported an average life expectancy of 3 to 4 months after the onset of ascites, whereas Henrikson (115) reported an average duration of 12.8 months in a series of 42

V
SUMMARY

1 A study was made of 386 patients with Laennec's cirrhosis of the liver in an attempt to understand the natural history of the disease. The course of the disease was analyzed with reference to the following data: antecedent factors, chief symptoms and signs, complications of cirrhosis, prognosis as to life after the development of specific signs, and causes of death. The medical literature pertaining to these aspects of cirrhosis of the liver was critically reviewed.

2 Certain antecedent or predisposing factors seem to be significant. An increased incidence of cirrhosis occurred in patients of Italian and Irish stock. However, there was no convincing evidence of hereditary predisposition. Characteristically Laennec's cirrhosis is a disease of late middle life (40 to 65 years). Males acquire the disease about 2 to 3 times as often as females, a fact which probably is explained by the higher incidence of alcoholism in males. Liquor handlers were the most frequent occupational group in this series. The history of alcoholism was obtained in 54 per cent and of syphilis in 16 per cent of the patients. Dietary factors were discussed with reference to the frequency of cirrhosis of the liver in the Orient, and with reference to recent experimental and clinical studies. In view of these studies it seems possible that the high correlation between the incidences of alcoholism and cirrhosis may be due to co-existing nutritional deficiency. The positive correlation between cirrhosis and malaria and enteric fevers also may be due in part to nutritional factors incident to these diseases. The past history of acute hepatitis, of exposure to hepatotoxins, of diabetes mellitus, and of thyroid disease was obtained in a small per cent of cases. As predisposing factors, these appear to be of lesser import.

3 The initial symptoms of Laennec's cirrhosis usually were indefinite. The most characteristic symptoms were related to the abdomen and gastrointestinal tract such as abdominal swelling and pain, anorexia, nausea, vomiting and flatulence. Weight loss occurred in one-half the patients. Hematemesis occurred in about one-quarter of the patients. Hemorrhagic phenomena, especially epistaxis, were observed commonly. Dyspnea, probably related to abdominal distention, was noted in one-fifth of the patients. Changes referable to the genitourinary tract such as nocturia, frequency, and sexual disturbances occurred in a significant number of patients.

4 The chief signs of cirrhosis of the liver were ascites, edema, jaundice, palpable liver and spleen, fever, and signs of collateral circulation. Ascites, the most frequent of these, was present in 78 per cent of the series. Peripheral edema was present in 61 per cent. It was suggested from available evidence that the level of the serum albumin is the critical factor in the formation of ascites and edema, whereas portal hypertension appears to determine the site of fluid transfer within the abdomen. Jaundice was a common sign, particularly during the terminal stages of the disease. It appeared in 65 per cent of the series. The presence of jaundice, as shown by survivorship curves, carries an ominous prognostic significance. Although 75 per cent had palpable livers, the average weight of the livers examined post-mortem was within normal

peries were performed died within the first month following the operation. This operative mortality has not been lowered appreciably in recent years. Hughson (121) reviewed the records of 26 patients with cirrhosis who had been subjected to various operative procedures at the Johns Hopkins Hospital. Sixteen patients were known to be dead at an average time of 22 days following the operation. Henrikson (115) studied the prognosis following operation in 31 patients with cirrhosis. Fifty-five per cent of these patients died within one month after operation.

The prognosis following omentopexy, should the patient survive the initial post-operative period, was at first considered to be better than without treatment. White (297) in 1906 reviewed 227 cases of cirrhosis in which omentopexy

TABLE 21
Cause of death in 213 fatal cases of Laennec's cirrhosis

CAUSE	NUMBER OF CASES	PER CENT OF CASES
"Cholemia"	77	36.2
Hemorrhage (hematemesis)	55	25.8
Post-operative	34	16.0
including peritonitis	3	
shock	3	
strangulated hernia	2	
broncho-pneumonia	1	
Pneumonia	22	10.3
Peritonitis, non-tuberculous	12	5.6
Pulmonary edema	7	
Post-paracentesis	5	
including peritonitis	1	
shock	1	
Cerebral hemorrhage	4	
Bacteremia	4	
Inanition	3	

Also 2 each—chronic pyelonephritis, convulsions, cardiac failure, erysipelas, hemorrhage into peritoneal cavity, 1 each—phlebitis of portal vein, acute pancreatitis, dehydration, epistaxis, ruptured mesenteric varix, meningitis, mastoiditis.

had been performed. Thirty-seven per cent of the patients were said to have been "cured" of ascites, and there was "improvement" in another 15 per cent. Recent studies, however, indicate that although improvement may be noted in individual instances, the average prognosis of patients with cirrhosis is not materially changed by operative therapy. In Hughson's series (121), one of 26 patients was known to be alive in good health $3\frac{1}{2}$ years after operation, but his liver had not been inspected at that time. Henrikson (115) calculated that the average duration of life following operation in 31 patients was only 5 months, and concluded that one should "hesitate to perform operations on any but those who present the best risks." Rowntree, Chapman, and Snell (230) considered the results of surgical therapy to be no better than those of medical treatment. This conclusion seems justified on the basis of the data presented elsewhere in the literature.

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limits Apparently the palpability of the liver depends on other factors as well as size, such as density of the organ and resistance of the abdomen to palpation The spleen, palpable in one-half the cases during life, is enlarged in about 80 per cent of cases at autopsy Vascular changes occurring in patients with cirrhosis were of two general types, namely those resulting from back pressure within the portal venous system (hemorrhoids), and those resulting from changes in the smaller arteries (vascular spiders) Signs referable to the cardiorespiratory system, such as cyanosis, clubbed fingers, and hydrothorax were discussed The high incidence of peripheral neuritis and of mental changes in patients with cirrhosis appears to be due to coexisting nutritional deficiency Fever, a sign not popularly associated with cirrhosis of the liver, was present in 24 per cent of this series

5 The chief complications of cirrhosis in this series were intercurrent infection, anemia, abdominal hernia, peptic ulcer, and portal vein thrombosis Tuberculosis occurred clinically in only 4 of 386 patients

6 The prognosis is grave in cirrhosis of the liver once signs of decompensation have appeared, such as ascites, jaundice, and hematemesis After the onset of ascites 47 per cent survived 6 months and only 32 per cent survived one year The spontaneous loss of ascites occurred in about 7 per cent of the cases After the onset of jaundice, 44 per cent lived 6 months and 26 per cent lived one year After the first hematemesis, 45 per cent lived 6 months, and 28 per cent lived one year

7 The chief causes of death in this series were cholemia, hematemesis, post-operative complications, pneumonia, and intercurrent infections

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CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY

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From The Mount Sinai Hospital

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I INTRODUCTION

A Purposes

Clubbing of the fingers and toes is a familiar clinical phenomenon, the nature of which has always been obscure. Hypertrophic osteoarthropathy, although seen less frequently than simple clubbing, has been the subject of numerous investigations designed to throw light on its pathogenesis. It is the purpose of this review to present all the accumulated data on these subjects in a manner that will clarify a new point of view.

B History

Curving of the finger nails was first described in a case of empyema by Hippocrates (126) in the fifth century B. C. Except for occasional casual comments (73), the phenomenon was not discussed until 1832 when Pigeau (236) wrote a detailed description of clubbed fingers which he found associated chiefly with pulmonary tuberculosis. In 1889, von Bamberger (15) reported several cases of a bone malady, preceded and accompanied by clubbing, and developing in the course of certain diseases of the lung and heart. In 1891 (16), he presented a classical description of the new syndrome. In 1890, Marie (191), in a comprehensive treatise, distinguished this bone disease from acromegaly with which it had been confused (80, 87).

C Names

These workers and many others proposed various names for what we know now as clubbing and hypertrophic osteoarthropathy. Among the names used for simple clubbing were watch-glass nails (177), parrot-beak nails (89), drumstick fingers (70, 73), serpent's head (89) or clock pendulum fingers (19, 222), Hippocratic fingers (19, 21, 29), essential dactylomegaly (66), hypertrophic acrodactylopathy (53), and club or clubbed fingers (71, 177, 182). These terms were derived from variations in the pathological anatomy of clubbing described more fully below.

Similarly, various names were proposed for the disorder now known as hypertrophic osteoarthropathy. The followers of Marie and von Bamberger referred to it as Marie's disease (65), Bamberger-Marie's disease (18) or the Marie-Bamberger syndrome (287). Other terms proposed but not in general use were toxigenic osteoperiostitis ossificans (289, 275), periostitis, osteitis or osteosis hyperplastica (8, 189, 275, 321), generalized osteophytosis (61), hyperplastic or hypertrophic osteopathy or osteoarthropathy (54, 57, 79), chronic osteopathy (27) or osteoarthropathy (133), secondary osteoarthropathy (123) or simply osteoarthropathy (230, 337) or osteopathy (282), peripheral hyperostosis (179),

osteoarthropathy deformans (245) hypertrophic-porotic osteo-periostitis (285) osteopathy dysplastica (188), pachyperiostosis (307), acromelic ensheathing periostosis (158) or simply ensheathing osteitis (251) benign tuberculous rheumatism (253), subacute tuberculous osteoarthritis (245), infectious hypertrophic osteoarthritis (72) and pulmonary hypertrophic osteoarthritis (241) Acropachy (73, 129, 275 303) was used as a term to designate either clubbing alone or with bone involvement A somewhat cumbersome expression suggested for the same purpose was acroelephantiasis ossea sive molle (313) The original name applied by Marie to the bone manifestations of clubbing was pulmonary hypertrophic osteoarthropathy (191) The term pulmonary was dropped when it became apparent that diseases other than those of the lung could produce the condition Thenceforth, the bone lesions were called either secondary hypertrophic osteoarthropathy (192) or simply hypertrophic osteoarthropathy (65, 83, 107, 135)

D Definitions

Clubbing of a finger or toe may be defined as a usually painless, uniform enlargement confined to the terminal segment Hypertrophic osteoarthropathy is an extension of the process of clubbing to more and more proximal parts of the extremities It takes its name from the striking enlargement of the bones caused by the deposition of new-formed periosteal bone and from the accompanying joint disorders

II CLASSIFICATION

The varieties of clubbing may be divided into three main groups symmetrical, involving all the fingers and toes, unilateral, involving the fingers or toes of only one extremity and undigital, involving only one finger Symmetrical clubbing may be further subdivided into hereditary and acquired and the latter according to its relation to the underlying disease pulmonary cardiac, hepatic, gastrointestinal, miscellaneous or doubtful Hypertrophic osteoarthropathy may occur as a feature of any of the varieties of clubbing or may be apparently idiopathic

A Acquired symmetrical clubbing

1 *Pulmonary* Symmetrical clubbing may occur in almost any variety of pulmonary, pleural, or mediastinal disease It is common and most pronounced in chronic suppurative conditions such as bronchiectasis (5, 245, 327), pulmonary abscess (141, 234, 245) and empyema (204 245, 284, 297, 322) It is seen less frequently in pulmonary tuberculosis (32 33, 34, 309, 337) and usually in the protracted cases I have seen it develop, however in as short a time as three months in a case of pulmonary tuberculosis with symptoms of activity for only six months (194) Clubbing may occur in any condition which produces a chronic pneumonitis such as pneumoconiosis (30), atelectasis because of intrabronchial obstruction (245), or external compression of the lung by chest deformities Such deformities may be produced by Pott's disease (9 32 107, 123, 179, 185, 317, 320, 325), rickets (89 287, 313), crushing injuries of the

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A. Acquired symmetrical clubbing

1 *Pulmonary* Symmetrical clubbing may occur in almost any variety of pulmonary, pleural, or mediastinal disease It is common and most pronounced in chronic suppurative conditions such as bronchiectasis (5, 245, 327), pulmonary abscess (141, 234, 245) and empyema (204, 245, 284, 297, 322) It is seen less frequently in pulmonary tuberculosis (32, 33, 34, 309, 337) and usually in the protracted cases I have seen it develop, however in as short a time as three months in a case of pulmonary tuberculosis with symptoms of activity for only six months (194) Clubbing may occur in any condition which produces a chronic pneumonitis, such as pneumoconiosis (30), atelectasis because of intrabronchial obstruction (245), or external compression of the lung by chest deformities Such deformities may be produced by Pott's disease (9, 32, 107, 123, 179, 185, 317, 320, 328), rickets (89, 287, 313), crushing injuries of the

chest (233), poliomyelitis (194), paralysis of the diaphragm (134) or diaphragmatic pleurisy (245) Kyphoscoliosis may be secondary to a primary thoracic disease capable of producing clubbing, such as empyema (284, 336) The end results, consequently, of some of these conditions may be difficult to distinguish from one another In those cases in which "Ayerza's syndrome" is due to a chronic pneumonitis (10, 245), clubbing is common, whereas, in genuine cases of pulmonary endarteritis (162, 260), it is rare It is occasionally seen in emphysema (274) but usually because of associated bronchitis or bronchiectasis Clubbed fingers have also been reported in pulmonary syphilis both congenital (279) and acquired (211, 243, 245, 271), in actinomycosis (335), and in hydatid cyst of the lung (162, 302) They are seen rarely in congenital cystic disease (162, 206) and in chronic passive congestion of the lung (71, 81, 185, 305) Clubbing is also rare in acute pulmonary infections such as lobar pneumonia (324) or bronchopneumonia (162, 267) It is of interest that clubbing may also occur in the erythremia of high altitudes (17) and that it subsides together with the other manifestations of this disease if the patient returns to sea level (205) Clubbing due to other causes may become exaggerated if the patient is brought to a high altitude (316)

Clubbing is frequently found in all types of primary bronchial, pulmonary, mediastinal (232), and chest wall neoplasms Among these are bronchogenic carcinoma (251, 266, 295), carcinoma of the thymus (202), lymphosarcoma (268), malignant mediastinal teratoma (276), neurinoma (160), pleural fibroma (97), sarcoma of the thoracic vertebrae (148), etc It is very common in pulmonary hemangioma (237, 254) and is also seen in Hodgkin's disease involving the lung or mediastinum (48, 229) Clubbing is also occasionally observed in cases of pulmonary metastases from extra-pulmonary neoplasms The primary tumor may be carcinoma of the breast (45, 150), adrenal (250), pharynx (253) or parotid (140), or a sarcoma, especially of the bone (41, 57, 233, 321) In cases of aortic aneurysm in which the effect of the aneurysm is similar to that of an expanding mediastinal tumor, symmetrical clubbing is also found (156)

2 *Cardiac* Certain diseases of the heart are also associated with clubbing In congenital heart disease with cyanosis it is very common (16, 109, 270, 274, 277, 316, 326) and frequently pronounced It is not seen in congenital heart disease without cyanosis, unless complicated by another disease such as subacute bacterial endocarditis or bronchiectasis (194) Clubbing is not uncommon in subacute bacterial endocarditis (16, 58, 96) In most of the reported cases, the lesions are confined to the left side of the heart (120) causing no large embolic foci in the lungs Clubbing may be the first sign of subacute bacterial endocarditis and its detection may therefore lead to the diagnosis (95) It has also been reported in one case of so-called acute bacterial endocarditis (117) The organism found, however, was streptococcus viridans Clubbing is rarely seen in the bacteria-free stage of subacute bacterial endocarditis (172) It is seen occasionally in chronic congestive heart failure (71, 185), the usual lesion being mitral stenosis (81, 305) I have also seen it develop in a case of congestive heart failure due to Graves' disease (194) Clubbed fingers were reported

in one very unusual case of myxoid tumor of the right auricle arising from the interauricular septum (55)

3 *Hepatic* Clubbing is also found associated with diseases of the liver (81, 291) It is quite common in that rare form of biliary cirrhosis called hypertrophic, cholangiolitic, or Hanot's (34, 51, 85, 100, 216, 230, 255) One author thought the enlarged liver compromised the lung (100), but there are many cases without demonstrable pulmonary involvement It is less frequently found in toxic cirrhosis (11), in biliary cirrhosis due to bile duct obstruction (255) and is rare in portal cirrhosis (255) A case of hemochromatosis (245) with secondary cirrhosis of the liver has been reported with clubbed fingers Another case of clubbing has been reported secondary to the cirrhosis of the liver and splenomegaly of chronic malaria (1) Cases of clubbing secondary to amyloidosis (224, 245, 280, 325) involving the liver and spleen have also been described In these cases the amyloidosis was caused by either chronic osteomyelitis or pulmonary tuberculosis and it is difficult to determine whether the cause of the clubbing was the amyloidosis or the original infection

4 *Gastro-intestinal* Clubbed fingers are also found in many abdominal conditions, most of which are accompanied by chronic diarrhea (299) Among these are chronic non-specific ulcerative colitis (196, 209, 269), chronic bacillary (196, 224) or amoebic (39, 165, 291) dysentery, regional enteritis (196), intestinal tuberculosis (194, 224), multiple polyposis of the colon (23, 40), neoplasm or Hodgkin's disease of the small intestine (194), and rarely, carcinoma of the colon (194) It is also frequently observed in cases of idiopathic steatorrhea (celiac disease (82), sprue (22, 146)) The Dutch have also described clubbing as a feature of so-called enterogenous cyanosis (52, 125, 293) In the cases with clubbed fingers, however, there was always an associated colitis, which may itself produce clubbing in the absence of methemoglobinemic cyanosis Methemoglobinemia alone is usually not associated with clubbing (24) Several cases of clubbing are also reported secondary to pyloric obstruction and gastrectasia (70, 145, 224, 241, 273, 330) caused either by a duodenal ulcer or a carcinoma of the pylorus In these cases the clubbing may recede after gastro-enterostomy or partial gastrectomy Clubbing has also been seen in ascaris infestation to subside following elimination of the worms (60)

5 *Miscellaneous* Isolated reports have appeared on symmetrical clubbing in conditions other than those already discussed For example, several cases are on record of the development of clubbing following thyroidectomy for Graves' disease (62, 74, 194, 303) In one of these cases there was also hypertrophic osteoarthropathy (303) Clubbing is rare in spontaneous myxedema and cretinism (73, 224, 245) A remarkable case (187) is reported in which clubbing developed in the course of a generalized febrile illness falling into the category of purpura rheumatica The clubbing receded with the patient's recovery Another observer (190) reports clubbing in a case of chronic cystopyelitis in which it waxed and waned with the activity of the underlying disease

6 *Doubtful* In addition to these apparently authentic cases, clubbing has been reported in some diseases in which the relationship is doubtful It has

been described, for example, in primary polycythemia (64, 162, 224, 245, 256) It is possible that these were really cases of secondary polycythemia due to congenital heart disease or chronic pneumonitis, in both of which clubbing is common In polycythemia vera, clubbing, if it occurs at all, is extremely rare It is well known also that syringomyelia is sometimes associated with vasomotor and sudomotor disturbances resulting in the so-called "main succulente" of the Morvan variety of the disease (208) The entire hand becomes enlarged rather than the ends of the fingers (130) In addition, ulcerations and inflammatory changes in the finger tips and traumatic periostitis of the bones (308) serve further to confuse the clinical picture Occasionally, nevertheless, clubbing is unquestionably associated with this disease (33, 277) A single case (181) of leprosy with clubbing in which some of the fingers were more involved than others is also reported In such cases, it is difficult to exclude the effect of chest deformities or of silent or unrecognized pulmonary disease The same comment might be made of an isolated case of Raynaud's disease (184), one of scleroderma (42), one of acrocyanosis (37), and one of chilblains (212), all with clubbed fingers I have observed a case of Raynaud's disease with clubbing in which there was silent unrecognized bronchiectasis (194) Isolated reports of rheumatic fever (51) or chronic nephritis (51) with clubbing must also be placed in the same category Occasionally such cases are found to be unrecognized subacute bacterial endocarditis The authenticity of all cases of this kind can only be established by unequivocal corroboration of the diagnosis by objective means or by autopsy, and also by the increase and decrease of the clubbing with the activity of the underlying disease Mere coincidence in isolated cases is not sufficient evidence of a causal relationship The absence of pulmonary disease as determined by x-ray, bronchogram, and if possible, bronchoscopy, as well as the absence of clubbing in any of the relatives of the patient, is valuable negative evidence

B Hereditary symmetrical clubbing

Clubbed fingers may occur in otherwise healthy people (34, 74, 132, 246, 261, 272, 275) and has sometimes been called familial clubbing (210) although this term also applies to clubbing which appears in families with tuberculosis (32, 74) Congenital clubbing (170, 215, 324, 332) is a misnomer since it has been shown that the abnormality is inherited as a Mendelian dominant trait (132) A better term, therefore, is hereditary clubbing This has been reported in twins (227) and may be found in association with other hereditary conditions Kollarits (147) has observed a case with pseudo-hypertrophic muscular dystrophy, and I have observed a similar case (194) Here, the question sometimes arises as to what part associated chest deformities due to muscular imbalance play in the production of the clubbing It is also possible that peripheral circulatory disturbances due to the muscular dystrophy play a part in the genesis of the clubbing It is most likely, however, that these are merely instances of associated hereditary anomalies

C Unilateral clubbing

The cases of unilateral clubbing form an interesting group. The most common cause of this is aneurysmal dilatation of either the arch of the aorta (105, 136, 200, 225, 245, 298), the innominate (27, 86, 113, 119, 180), or the subclavian artery (19, 21, 26, 75, 108, 118, 200, 213, 218, 238, 239, 280, 298). If both subclavian arteries (98) are involved one may then observe bilateral clubbing of the upper extremities. This must be distinguished from ordinary symmetrical clubbing observed in some cases of aortic aneurysm simply because of an expanding mediastinal mass (156). A single case (249) of unilateral clubbing has also been reported in association with a brachial arterio-venous aneurysm. Most cases of arteriovenous aneurysm, acquired (168) or congenital (193), however are not accompanied by clubbing, although they may produce enlargement and increase in length of the entire extremity. An interesting case of unilateral clubbing involving all the fingers and accompanying phlebectasia and venous varicosities of the involved extremity was reported by Souques (281). I reported a similar case (195), except that the thumb, index and middle fingers were more markedly clubbed than the other two. The status of the arteries in these cases was not known. A case of unilateral clubbing has been reported as a sequel of recurrent subluxation of the shoulder (143), and, in another case, of subluxation of the shoulder caused by an axillary tumor (244). Here again the status of the axillary artery was unknown. Cases of unilateral clubbing (195, 244) have also been reported in association with carcinoma of the apex of the lung involving the sympathetic ganglia (so-called Pancoast tumors (226)). In this connection, apical tuberculosis (224) and occasionally empyema (110), by traction and pressure on the nerves passing over the apex, may apparently increase the clubbing on the side involved. Moebius (203) reported an increase of the clubbing of the fourth and fifth fingers of one hand in a case of symmetrical clubbing due to pulmonary disease, in which the patient developed an ulnar neuritis. Majdracoff (186) described a similar case in which only the thumb was involved. Maury and Dühring (193) also reported a case of bilateral clubbing in which it was more pronounced on the side of a coincidental neuroma of the brachial plexus. After resection of this neuroma the nail growth on the side of the previous tumor became slower than on the other side. A case of unilateral clubbing with erythromelalgia of the corresponding hand has also been reported (69). Unilateral clubbing and hypertrophic osteoarthropathy of a lower extremity have been seen secondary to lymphangitis (142).

D Unidigital clubbing

Cases of unidigital clubbing (322) have also been described. The first such case was reported by Ogle in 1865 (219). The clubbing developed after a blow on the arm which apparently injured the median nerve. Similar clubbing has appeared after local trauma to the finger (162). Unidigital clubbing has been reported to occur in Boeck's sarcoid (162), in felons (162), and in tophaceous gout (162). Many conditions involving the fingers, however, such as gout, osteoarthritis with Heberden's nodes, scleroderma, Raynaud's disease, brachy-

dactly, etc are accompanied by trophic changes and bony deformities which must be carefully distinguished from true clubbing. Bilateral undigital clubbing, especially of the thumbs, is hereditary (214)

E Clubbing with hypertrophic osteoarthropathy

Although it was at one time thought that clubbing and hypertrophic osteoarthropathy might be independent phenomena, (28, 171) it is now generally recognized that the bone changes arise from the same causes as the clubbing and represent a more advanced stage of the process. Hypertrophic osteoarthropathy, however, is considerably less common than simple clubbing. It was at one time confused with acromegaly (80, 87, 286) although the two diseases may very rarely coexist (259, 265). It is most often, like clubbing, found with chronic pulmonary diseases such as lung abscess (234), tuberculosis (3), bronchogenic carcinoma (59) and bronchiectasis (16). Hypertrophic osteoarthropathy has also been described by various observers to occur in the rat (296), the dog (12, 122), the horse (14, 173), and even the lion (14), usually in the wake of a chronic pulmonary infection, most commonly tuberculosis (173), or of a pulmonary neoplasm, spontaneous (122) or experimental (296). The occurrence of hypertrophic osteoarthropathy, however, is not confined to pulmonary diseases. It may be found in any condition with which clubbing is associated, such as congenital heart disease (16, 274), cirrhosis of the liver (85, 216, 230, 291), chronic diarrhea (224, 291, 299), etc. Bone changes may occur in hereditary (210, 246, 264, 275, 319) and even in unilateral (75) clubbing, but whether they are in every case characteristic of hypertrophic osteoarthropathy is disputable.

F So-called idiopathic clubbing and hypertrophic osteoarthropathy

There is a group of cases in which clubbing with or without bone changes has been reported to appear in the absence of any ascertainable cause (4, 20, 92, 164, 217, 221, 247, 282, 290, 301, 322, 333). These cases may be divided into several categories. In the first, are cases of hereditary clubbing unrecognized as such (68). In the second, are cases of silent pulmonary lesions, such as bronchiectasis or neoplasm, in which the clubbing and bone changes are the first and outstanding manifestations of the disease (57). In the third group (6, 7, 46, 90, 134), there are several cases in which no evidence of any underlying disease appears for years despite the presence or progressive development of the clubbing and of the hypertrophic osteoarthropathy. No such case has been reported with an adequate autopsy record (178), and the underlying cause of these changes must therefore remain obscure.

III CLINICAL FEATURES

A Onset

Clubbing as well as hypertrophic osteoarthropathy may begin at any age. It is described in infants (84, 133, 313) and in the very old (301). The sex distribution of clubbing depends on that of the underlying diseases. Because

of the prevalence of pulmonary tuberculosis, which is more common in females, clubbing was formerly seen more often in women than in men (36, 236) With the decreased incidence of pulmonary tuberculosis, however, the reverse is now found (233) Clubbing is usually so gradual in onset that the patient seldom becomes aware of any change in his fingers or toes until it becomes very pronounced, or, more commonly, until it is observed by a physician The changes may take years to develop, or, more rarely, they may appear within one week (245) of the onset of the underlying disease

B Symptoms and signs of clubbing

Clubbing is rarely accompanied by any subjective symptoms A feeling of warmth, excessive sweating or a burning sensation (194) may be experienced in the finger tips In very acute clubbing, there may be pain (310, 323), although this is very unusual Occasionally, pain may be caused by coincidental paronychia (194) One patient regularly noticed a vesicular eruption along the finger tips at the time of exacerbation of the clubbing and of his underlying lung abscess (194) Patients also occasionally notice increased rapidity of growth of the nails (318), cuticles (194), or both In most instances, however, simple clubbing is quite asymptomatic (236)

Although clubbing concerns all the tissues of the fingertips it is usually first detected because of thickening of the fibro-elastic tissue of the nail bed (8, 81) Ordinarily, the plane of the proximal portion of the nail makes an angle of about fifteen degrees with the dorsal plane of the bone (182) This angle may be obscured by the pushed-back eponychium or by a paronychia (182), but the plane of the bone may be determined by a rectilinear distal projection of the dorsal plane at the knuckle with the distal phalanx flexed, the finger tip being viewed from the side (194) There are great variations in the degree of sagittal curvature of the nail itself, and occasionally exaggerated curvature will be mistaken for clubbing (194) This error cannot be made, however, if a normal angle between the plane of the nail root and that of the bone is observed A decrease in that angle is the first sign in clubbing (182) If it becomes obliterated or negative the clubbing is usually manifest

Various clinical forms of clubbing have been described and it is now apparent that these variations are not attributable to different underlying diseases or mechanisms as was originally thought (64, 230), but rather to differences in the initial anatomy of the finger tips and in the degree of clubbing In early clubbing, for example, there may be uniform thickening of the nail bed tissue without much tilting of the base of the nail ("watch-glass" type) (177) If the nail is naturally tapering and firmly fixed laterally to the underlying tissue, it may assume an exaggerated lateral and longitudinal convexity together with dorsal basal tilting ("parrot-beak" type) (89) If there is a hyperplasia of the other tissues of the finger tip so that it becomes bulbous and larger in circumference than the second phalanx, the name, "drumstick finger," (70, 73) is applicable There are many variations of this relatively advanced stage For example, there may be marked tilting of the nail without much thickening

and even with atrophy of the volar portion of the finger tip (194), or conversely, a pronounced increase in the size of the volar pad without commensurate change in the nail bed (44), although these are rare forms. The increase in size may be greater anteroposteriorly or laterally. In the latter instance, the terms, "serpent's head" (89) or "clock-pendulum" (19, 222) fingers, have been applied. There may be thickening of the entire finger as well as of the tip if there is a hypertrophic osteoarthropathy involving the phalanges. The French use the term, Hippocratic fingers (19, 21), generically, although Hippocrates wrote only of curving of the nails (126). The expression, club or clubbed fingers (62, 71, 182), has been derived from the relatively advanced form, and has been commonly extended to apply to all varieties.

In addition to the increase of the area as well as the thickness of the nail bed in clubbing, there is a corresponding increase of the area and thickness (81) of the nail itself including the portion beneath the eponychium (8, 317). The nail tends to be more resilient (317), especially at its base. This is usually more prominent in early than in late clubbing and in young rather than in old people (194). The longitudinal ridging of the nail is frequently exaggerated in clubbing (81) and the nail may become very brittle (317). In rare instances, it may develop an irregular pigmentation and roughening of its surface (194). One case (53) of complete necrosis of all the nails is reported. It is difficult to determine whether some of these features are part of the phenomenon of clubbing or are added variants due to the presence of a generalized debilitating disease or of local infection. Because of their increased rate of growth (194, 295, 318), the nails usually require more frequent filing or clipping. The increased size of the eponychium and adjacent skin covering the posterior surface of the nail tends to obscure whatever portion of the lunula was visible before the onset of the clubbing (34, 81). The increased rate of growth of the cuticles, especially if they are not properly cared for, cause hang-nails to be formed very readily (261). These may become infected (194), so that acute and especially chronic paronychia are not infrequently found in clubbed fingers. All the fingers of both hands may be involved, although it is more usual to see only one or two fingers affected.

The changes in clubbing are rarely confined to the nails. The skin over the base of the nail and over the volar surface of the distal phalanx is often flushed a bright pink (89). This flush also involves the nail bed and may impart a rose red color to the nail (191). It is more extensive and brighter than that frequently seen in normal fingers and may contrast sharply with the pallor of the remainder of the finger (194). As in normal fingers, the flush tends to fade and become cyanotic when the fingers are cool (194). Because of underlying debilitating disease, some of the patients with clubbed fingers are poorly nourished and susceptible to cold. Their fingers, therefore, may appear cooler at times than normal (270). In such fingers, as in normal cool fingers, blanching of the flush by pressure will become obliterated very slowly, but this is hardly, as one author believed (93), a fundamental characteristic of clubbing. The flush may appear cyanotic, also, in the presence of arterial anoxemia (194). It may be less

prominent if the patient is anemic (194) It may appear in the earliest stages of clubbing, and does not necessarily become more pronounced as the clubbing advances (194) The skin over the base of the nail may become thin and shiny and somewhat more tightly stretched with obliteration of the usual creases (194) Because of the bulbousness of the volar pad, especially in long standing cases and in patients in the growing years, as in congenital heart disease, the exigencies of use (194) may bring about dorsiflexion of the distal phalanges with hyperextensibility (163, 245, 317) of the distal phalangeal joints Some observers have noted an apparent increase in the length of the clubbed fingers especially in the growing child, although this is very difficult to prove (64, 185)

Except in unilateral cases, clubbing of the toes develops nearly always *pari passu* with clubbing of the fingers (162) Because, however, of the greater variation in the shapes of the toes, as well as the greater frequency of deformities due to shoes, clubbing of the toes is more difficult to recognize, especially in its early stages (194) Normal toes, moreover, frequently appear clubbed (162) Early clubbing is perhaps best recognized in the big toes (317) where the distal phalanx is more nearly like that of the fingers Definite evidence of clubbing, except in the advanced cases where the changes are obvious, can only be adduced from successive measurements of the area or diameters of the toe nails Clubbing of the nose, ears, eyelids, and malar region are mentioned by several authors (38, 144, 163, 304, 322), although obvious anatomical considerations make it very difficult to be sure of the development of such clubbing in any given case

Hereditary clubbing differs from the other forms in that it may involve the different fingers or toes in varying degree (132, 196, 324) Some of the fingers may be spared and only two or three fingers of each hand symmetrically involved The thumbs are nearly always included among the clubbed fingers (132) They may be the only fingers affected (214), in which case the clubbing must be distinguished from hereditary brachydactyly of the thumbs (162) The toes are also usually involved in hereditary clubbing (246) and I have seen symmetrical clubbing (194) of the big toes only, without involvement of the other toes or of the fingers It should be emphasized here that in normal embryos all the fingers and toes appear clubbed (252), although it is doubtful that hereditary clubbing is merely arrested development A peculiar feature of hereditary clubbing is that, although it is usually present as long as the patient can remember, it sometimes becomes much more pronounced in middle life (264, 272, 324) In one such case (195, 272), the increase in clubbing was noted to be coincidental with the development of essential hypertension

In unilateral clubbing, differences in the length of the terminal phalanges may be observed by comparing the two sides It is possible that such changes take place in symmetrical clubbing as well, although here it is much more difficult to determine especially if the clubbing develops during the growing period In unilateral clubbing, the clubbed finger tip in any given case may be shorter (195) or longer (195) than the contralateral, or there may be no difference in length (195)

C Symptoms and signs of hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy may appear from six months to twenty years after the onset of the underlying disease (89). It is often asymptomatic especially in its earlier stages, its presence being detectable only by x-ray. In the later stages there are frequently aching pains and tenderness along the shafts of the long bones and about the joints (16, 163, 289). The pains are usually aggravated by cold or movement (289) and assuaged by warmth and rest. They have been reported by different observers to become either more (224) or less (101) severe at the time of the menstrual period. In an occasional case in which clubbing and hypertrophic osteoarthropathy develop very rapidly, the pains in the extremities may be quite severe (89) and may precede x-ray changes in the bones. This disease may hence be mistaken for rheumatoid arthritis or osteoarthritis (121, 194, 245), especially in cases in which hypertrophic osteoarthropathy is the first manifestation of a silent pulmonary condition (57, 283). This acute form is seen sometimes in children (89) but is also occasionally observed in adults (194). Spontaneous fractures are not uncommon, presumably because of the extreme osteoporosis in some cases (245). There is usually no increase in the length of the bones in adults. In children, it is believed by some observers that the extremities increase in length above the increase of normal growth (210). Because of individual variability, however, this is difficult to prove. The joints in a case of hypertrophic osteoarthropathy may develop moderate effusions and some limitation of motion (233). In advanced cases, they may become partially or completely ankylosed (245). Because of the increased size and weight of the bones, especially at their peripheral ends, there is a heaviness of the extremities which causes awkwardness of gait and clumsiness in the movement of the hands and fingers (16, 89, 163, 317).

The manifestations of hypertrophic osteoarthropathy are not confined to the bones and joints. There may be definite muscular weakness (163) and slight edema and hypertrophy of the subcutaneous tissues of the extremities (89, 163). There may be increased sweating (4, 89) and burning sensations in the skin of the hands and feet, especially the latter (16). The skin may become thickened (99, 317) and develop increased pigmentation (295) or eczematoid lesions (89, 163, 317) and increased hair growth (8, 295) including the mustache (283). Several curious cases (8, 153, 266, 275, 307) have been described in which there was a pronounced increase in the thickness of the skin over the palms of the hands, the soles of the feet, and in some over the face. In one such case, the clubbing was apparently hereditary (275), whereas in the others, the clubbing and hypertrophic osteoarthropathy were secondary to pulmonary disease (153, 266).

D Recession of clubbing and hypertrophic osteoarthropathy

It is characteristic for both clubbing and hypertrophic osteoarthropathy to wax and wane with the activity of the underlying disease. Thus, complete disappearance of clubbing and sometimes of associated bone changes have been described after spontaneous (67, 315) or surgical (322) drainage, or radiotherapy

(245) of an empyema (110 204 245 297) or lung abscess (196 234) after surgical (194) x-ray (25) or collapse (phrenicectomy) (245) therapy of bronchiectasis or after irradiation (31 232) or surgical removal (97) of a mediastinal or pulmonary tumor. They have also been observed to recede after spontaneous recovery from pneumonia (47) diaphragmatic pleurisy (245) or pulmonary tuberculosis (67 245 305) Recession has also been seen after collapse therapy in tuberculosis whether surgical (162) or by phrenicectomy (162) or pneumothorax (162) In pulmonary syphilis clubbing has decreased with antiluetic therapy (271) Recession has also been seen following endobronchial removal of a foreign body (245) or a neoplasm (194) Clubbing may subside after release of venous obstruction by irradiation of a mediastinal neoplasm (48) It may subside after partial gastrectomy or gastroenterostomy in pyloric obstruction (70 145) or after resection of the ileum in regional ileitis (194) It also disappears after successful medical (146 194) or surgical (125 194) treatment of amoebic dysentery ulcerative colitis sprue or ascariis infestation (60) In post-thyroidectomy myxedema the administration of thyroid may cause some decrease in the clubbing and hypertrophic osteoarthropathy (303) In chronic mountain sickness recession may be effected by descent to sea level (205) Diminution of clubbing with subsidence of cystopyelitis (190) or purpura rheumatica (187) has already been discussed In unilateral cases due to aneurysm successful ligation (108 280) or compression (239) may cause the clubbing to diminish In some cases it may disappear spontaneously (86) with or without the aid of antiluetic therapy (118 119) presumably because of thrombosis and obliteration of the aneurysm In one case in which there was venous obstruction partial recession was induced by continued elevation of the arm (280) Complete disappearance is never seen in hereditary clubbing and rarely observed in such diseases as subacute bacterial endocarditis or cirrhosis of the liver where the underlying process is usually progressive Yet a case of subacute bacterial endocarditis in a tailor is described by Libman (172) in which subsidence of the clubbing was made apparent by a decrease in the size of the thumb needed as the patient went into a bacteria-free stage Another case is reported (Baehr) (11) in which clubbing receded together with the other manifestations of subacute bacterial endocarditis after treatment with sulfanilamide and hyperthermia

Clubbing may be the barometer of the underlying disease (175) and may increase and decrease several times with exacerbations and remissions (236) In one case (194) of lung abscess with frequent exacerbations of activity in the form of fever chills and pain in the chest the enlargement and burning sensations in the finger tips appeared before the onset of each exacerbation only to recede nearly but not quite to normal in each interval This patient when last seen had had eight such exacerbations There may be similar exacerbations and remissions of hypertrophic osteoarthropathy (148 189 233) with variations in the activity of the underlying disease In view of all these features it is apparent that all therapy must be directed at the underlying disease and the local complaints treated palliatively and symptomatically

IV ROENTGENOLOGY

A Phalanges

The x-ray changes in the distal phalanges are variable, depending on the nature of the underlying disease and on the stage in the development of the clubbing or bone disease. In the earliest stage of clubbing, there may be no x-ray changes whatsoever in the terminal phalanges (176). In the more advanced cases, there may be merely an increased flare of the ungual process of the terminal phalanx (139). It is possible that in some cases, especially if the clubbing develops during the growing period, the terminal phalanges become hypertrophied and longer than normal (64, 185). This is difficult to demonstrate in symmetrical clubbing but has been seen in the unilateral variety associated with phlebectasia (195). As the disease advances, however, atrophic changes may develop in the terminal phalanges, ranging from simple osteoporosis (110, 139) to complete resorption (174, 188, 221, 275, 277, 319, 327) of several or all of the end phalanges. This may occur in clubbing due to pulmonary disease (294, 327) or to congenital heart disease (174, 277), or in hereditary clubbing (77, 188, 275, 319). Hypertrophic osteoarthropathy with periosteal proliferation usually involves bones proximal to the phalanges. In rare instances, however, all the phalanges including the terminal ones may be ensheathed by new-formed periosteal bone (151, 295).

B Other bones

Extensive roentgenological changes in bones other than those of the terminal phalanges are observed with the development of hypertrophic osteoarthropathy. Those involved earliest and most frequently are the tibiae, fibulae, radii, ulnae, femora, humeri, metacarpals and metatarsals. Later the phalanges, clavicles and pelvis may be affected. The tarsals, carpals, vertebrae, ribs and scapulae are rarely, and the mandible and skull almost never involved (89). At first, new formed periosteal bone is seen along the shafts of the long bones (263). This is usually thickest in the region of the peripheral epiphyses and is more pronounced at the lines and points of muscular insertions, forming osteophytes (134). In the early stages of the process there may be no discernible changes in the original bone (263). One author (103) describes an increase in the density of the cancellous portions of the involved bone. In hypertrophic osteoarthropathy in children it is thought by some that the growth process in the bones is stimulated and that an abnormal increase in the length of the long bones takes place (210). Individual variation makes this very difficult to demonstrate. In the more advanced stages of the disease both in children and in adults, most observers (134, 233, 263) find progressive osteoporosis of the cancellous portion and thinning of the cortex of the original bone. This process is also more pronounced in the region of the peripheral epiphysis than in the diaphysis or proximal epiphysis (61). Eventually osteoporosis of the new-formed periosteal bone may also be seen (263). It is difficult to determine how much of this bone resorption is due to the presence of a debilitating underlying disease and how much

is part of the process of hypertrophic osteoarthropathy Tree-trunk layering (148, 189, 233) of new formed periosteal bone may be observed by x-ray in cases with exacerbations and remissions of the underlying disease

In some cases of hypertrophic osteoarthropathy, the bone changes reported are very atypical This applies especially to the increase in thickness and length observed in some cases of hereditary clubbing (188, 264, 319) and to the bone atrophy in unilateral clubbing (75) In the absence of definite periosteal proliferation, the diagnosis of hypertrophic osteoarthropathy always remains in some doubt Moreover, periosteal proliferation (245) may occur with trauma (308), varicose veins (111), lymphangitis (54, 128) syphilis (137), and other conditions which may coexist with diseases producing clubbing Such periostitis must be carefully distinguished from true hypertrophic osteoarthropathy

V PATHOLOGY

A Difficulties

The pathology of clubbing has received comparatively little attention One of the reasons for this is the difficulty of obtaining and preparing specimens The paucity of reports on the histopathology of clubbing is hence in direct contrast to the multiplicity of conflicting interpretations

One of the difficulties of interpretation is to be found in the association terminally of clubbing with other pathological processes Thus, on the basis of a single specimen in which there was edema of the connective tissue, Campbell (47) considered this edema to be the essential pathological change in clubbing In another single case of generalized lymphosarcomatosis, Schirmer (268) described a blue-staining mucinous tissue which replaced the connective tissue of the clubbed finger It is impossible here to exclude terminal and post-mortem changes

Another difficulty has been inadequate knowledge of the normal histology of the finger tip It is well-known that after longitudinal section of a finger and especially after fixation, the clubbing may seem to disappear because of shrinkage (79 194, 207 322) It is only after comparison of such a finger with a normal one similarly treated that the difference in tissue distribution becomes apparent (81, 194) Thus, Buzzard (44), finds only hypertrophy of the volar pad of the finger tip in his single case of clubbing, although there is also an obvious increase in the connective tissue of the nail bed in his illustration This would have been evident had he compared his section with that of a normal finger tip similarly prepared

B Pathology of clubbing

It has become clear from various reports, that clubbing is characterized by increased proliferation of all the tissues of the finger tip (8 152, 177, 245, 274) This is most apparent in the fibrous elastic tissue of the nail bed (295), although it also takes place in the fatty connective tissue of the ball of the finger (44, 245) Most observers also find dilatation and increased thickness of the walls of the small blood vessels of the finger tip (8, 81, 91, 152, 245, 277, 312), as well

as new formation of capillaries (253) The number of arterio-venous anastomoses per unit of tissue is within normal limits (194), although qualitative changes in these structures have not been studied There is an increase in the area of the nail and skin corresponding with the increase in volume of the underlying tissues (8, 81) An increase in the thickness of these epidermal tissues has also been observed (8, 81, 91, 300), although the wide range of normal variation makes this difficult to demonstrate There is also increased thickness of the periosteum and of the ungual process of the bone itself (194, 228) In advanced cases, however, atrophy (152) and even complete resorption (174) of the bone may take place The latter process, unfortunately, has never been studied histologically

C Pathology of hypertrophic osteoarthropathy

The gross pathology of the bones in hypertrophic osteoarthropathy has been studied chiefly by the examination of lye-digestion specimens (16) Irregular, porous, rough accumulations of new-formed periosteal bone in confluent islands with geographic borders are found along the shafts of the long bones, which may be completely ensheathed (8, 16, 251, 285) The pores are larger in the long bones than in the smaller bones (295) This new bone formation is usually thickest in the region of the peripheral epiphysis (8) and is more pronounced at the lines and points of musculo-tendinous insertions (16, 61) This has led some authors to consider hypertrophic osteoarthropathy to be a generalized extension of local osteophyte formation (61) The frequently found osteoporosis of the cancellous portion and thinning of the cortex of the original bone have already been discussed (8, 61, 88) When this process of osteoporosis extends to the new-formed periosteal bone, a thinly trabeculated space may be found between the cortex and the new periosteal bone (61, 228) Several such spaces may be found in tree-trunk layers (148, 189) in cases subject to exacerbations and remissions Pathological fractures are occasionally seen (245) The joint capsules and synovial membranes may be thickened (306) with or without co-existing joint effusions (285) There may be fibrous or bony ankylosis (61) and occasionally the cartilages of the large joints are found to be symmetrically eroded (306)

Microscopically, the periosteum may be thickened (300) and show increased proliferation of the cambium layer (61) It may contain accumulations of lymphocytes and round cells containing oxyphilic granules (61) There may also be small hemorrhages and areas of edema and vasodilatation not unlike those seen in local osteophyte formation (61) The pores seen in the new-formed bone after lye-digestion are found to contain periosteal bands (295) in which there are numerous blood vessels (16, 91, 98, 251, 285) and Sharpey's fibres (61, 251, 285) With the development of increased osteoclastic activity and osteoporosis (148, 251), the trabeculae of the cancellous bone become thinner and more widely spaced (45, 285) The cortex of the old bone becomes eroded (285) Later, lacunae appear in the new-formed periosteal bone, forming trabeculae which also become progressively resorbed (61) The Haversian system of the

new-formed bone is then seen to be disrupted (285) and is, together with the lamellae, generally perpendicular to that of the old bone (13, 228). The bone cells and bone plates of periosteal bone are also distorted (285). In the later stages, the new bone is separated from the old cortex by a thinly trabeculated space (61). There may be several such spaces producing layers of new-formed periosteal bone. Occasionally, bone metastases from malignant pulmonary neoplasms will be seen in the bones affected by hypertrophic osteoarthropathy. These metastases are found most often in the old compact and new-formed periosteal bone (250-266). The marrow of both the new-formed periosteal bone and of the old bone is richer and more vascular in the areas of active periosteal proliferation and more fatty in the inactive areas (61-163). Other changes in the bone marrow such as eosinophilia, etc., are dependent on the nature of the underlying disease, rather than a part of the process of hypertrophic osteoarthropathy. The synovial membranes may present fibrinoid degeneration and sub-synovial congestion and collections of lymphocytes and leukocytes with eventual proliferation of granulation tissue and pannus formation (61-245). Pannus pressure may cause fibrinoid degeneration of the cartilage (325), with splitting and erosion, and fibrous or bony ingrowth, producing ankylosis (61).

D Chemical pathology

Chemical analyses of the bone with modern methods (Rénon and Géraudel (251)) have failed to confirm the variations from the normal reported by Chabrière (50) in hypertrophic osteoarthropathy. Parkes-Weber (228), however, describes a case in which the new-formed periosteal bone was less deeply stained with hematoxylin than the old bone. He interprets this as evidence of decreased calcium content of the new bone.

VI PATHOGENESIS—ANIMAL EXPERIMENTATION

Many attempts were made to reproduce hypertrophic osteoarthropathy in the experimental animal. Von Bamberger (16) instilled material from a human lung abscess into rabbits by rectum and failed to produce bone changes. Pus from abscesses and lymph glands and also cultures of various organisms, including the tubercle bacillus, were injected intravenously in rabbits and guinea pigs by Dor (72). He produced a purulent arthritis which he confused with hypertrophic osteoarthropathy. Phemister (234) also injected cultures of various organisms intravenously in animals but was not successful in producing bone changes. Compere Adams and Compere (56) produced pulmonary abscesses in dogs by paraffin injections into the lungs but also failed to achieve bone changes. Harter and Churchill (116) were also unsuccessful in producing hypertrophic osteoarthropathy by tying off bronchi in cats and monkeys. Stephens (288) was unable to produce clubbing or bone changes in animals by causing chronic congestion.

Hypertrophic osteoarthropathy was successfully produced experimentally by anastomosis of the left and adjacent main pulmonary artery to the left auricle in dogs (Mendelwitz and Leslie (197-198-199)). This produced a lesser circuit

shunt simulating the circulatory status observed in congenital heart disease with cyanosis. Shunts from 13 to 46% of the ventricular output were produced by this method. These shunts were accompanied by no change in the ether circulation time, venous blood pressure or oxygen consumption per minute. There was a consistent decrease in cyanide circulation time. In the smaller shunts there was little change in blood volume, whereas in the larger ones there was an increase of both cell and plasma volume. The blood pressure either became lower or remained essentially unchanged. The most significant finding associated with the development of hypertrophic osteoarthropathy was an increase in systemic cardiac output, the blood flow through the lungs remaining comparatively normal.

VII PATHOGENESIS—CLINICAL PHYSIOLOGY

A Arterial, venous and capillary blood pressures

Methods for the accurate study of peripheral circulation have only recently been developed. For this reason, Roncato, in 1927 (258), using inadequate methods came to erroneous conclusions concerning circulatory changes in clubbed fingers. He maintained that the venous pressure and capillary pressure were raised and the arterial pressure lowered in clubbing. It is now generally accepted that the antecubital venous pressure in uncomplicated clubbing is usually within normal limits (162, 194). It is also generally recognized that the brachial arterial pressure in uncomplicated clubbing is normal, unilateral cases excepted (195, 196). The only accurate method for measuring capillary blood pressure is the direct method of Landis (155) and to my knowledge no studies of capillary blood pressure by this method have been made in clubbed fingers.

B Capillaroscopy

With the advent of capillaroscopy, many studies on clubbed fingers were made with conflicting results. Thus, de Haas (112) found capillary stasis with decreased flow and constricted capillaries, Rominger (257) described dilated or aneurysmal loops, Leader (161) reported lengthened thin loops with granular streaming, whereas Wright and Duryee (334) and others (159, 245, 248) reported variable changes. It is not difficult in the light of modern physiology to explain some of these apparent discrepancies. The blood flow to the extremities has an enormously wide normal range under varying conditions. This is due to the control of the calibre of the arterioles and arterio-venous anastomoses exercised by the autonomic nervous system. In general, cold and such emotions as fear tend to decrease blood flow, whereas warmth and pleasurable emotions tend to increase it (169). Unless, therefore, capillaroscopic studies are carried out under standardized conditions, variations with environmental temperature and emotion will create differences in flow and in the appearance of the capillaries, superimposed on whatever fundamental changes have taken place because of the clubbing. In addition, local factors frequently affect the appearance of the capillaries. Significant differences are observed, for example, if the cuticle is habitually pushed back or if there is a low grade chronic paronychia infection (194).

All these variables make the capillaroscopic studies of clubbed fingers thus far reported of doubtful value

C Blood flow

1 *Skin temperature* Methods for the determination of blood flow have also been developed recently and some of these have been used in the study of clubbed fingers. It has been shown that skin temperature, measured most conveniently with the electric thermocouple, is generally proportional to blood flow (167). On the basis of such measurements made under unstandardized conditions de Haas (112) concluded that there was a decrease in blood flow in clubbed fingers. These conclusions, however, are subject to the same criticism already leveled against capillaroscopy with reference to the wide normal variations with changes in environmental temperature and emotion. In my own measurements of skin temperature in normal and clubbed fingers (195), I was unable to confirm de Haas's findings. After release of sympathetic tone, moreover, there were no significant changes in the skin temperatures of normal as against clubbed fingers or in the gradient of temperature from the base to the tip of the finger.

Since the relation between skin temperature and blood flow is a curve, the asymptote of which is the temperature of the arterial blood, any conclusions concerning blood flow adduced from skin temperatures in warm fingers are subject to error. Thus, once the skin has been warmed by the blood to the maximum, a further increase in flow will not produce a corresponding increase in temperature (194). In order to measure blood flow under standardized conditions (235), that is after release of sympathetic tone by rest and body warming, some other method must be used.

2 *Plethysmography* Plethysmographic methods for the study of blood flow through the finger tips have recently been devised by Grant and Pearson (104), by Wilkins, Doupe and Newman (329) and by Turner, Burch, and Sodeman (311). The method generally used has been a modification of the Hewlett and van Zwaluwenburg (124) method for the arm, in which the increase in volume per minute is measured after venous obstruction. Turner et al (311), measured the pulse volume in the finger tips of patients with hereditary and acquired clubbing and found it to be below normal in hereditary and within normal limits in acquired clubbing. These measurements, however, bore no quantitative relationship to blood flow and were made under unstandardized conditions. These workers have recently adopted the principle of Hewlett and van Zwaluwenburg (124) in their studies (43). All plethysmographic methods require elaborate apparatus which makes them too cumbersome for work at the bedside (196). There are also technical objections and sources of error which make them less applicable for the study of blood flow in the finger tips (196). The normal range of variation after release of sympathetic tone reported by Wilkins et al (329) was nevertheless in accord with that which I found with the calorimetric method (196). In a single case (195), moreover, studied with Grant and Pearson's (104) method, the results were also at least qualitatively, in accord with those obtained calorimetrically.

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E Studies in hereditary clubbing

In hereditary clubbing, both the blood flow per sq cm and the pressure gradient were within normal limits (196). In one case, only three fingers of both hands were clubbed. There was no essential difference between the blood flow per sq cm or the digital arterial pressure of a clubbed and those of a normal finger (196). Abnormally high blood flow or digital arterial pressure after release of sympathetic tone were not found in other clinical conditions such as aplastic anemia, Graves' disease, essential hypertension, or acromegaly (196). They were also absent in various chronic infections not associated with clubbing such as rheumatoid arthritis, chronic pyelonephritis and chronic salpingitis (196). In malignant hypertension, however, there may be a decreased brachial-digital pressure gradient (195, 220).

F Studies in unilateral clubbing

In unilateral clubbing, the clinical and physiological findings reported by various observers were extremely variable. The involved hand, for example, might either be colder (105, 113, 180, 195, 239) or warmer (195) than the uninvolved or there might be no difference in temperature (195). The strength of the pulse and the height of the blood pressure might either be greater (157, 195, 200, 238) less (19, 21, 26, 27, 75, 105, 113, 118, 119, 136, 180, 195, 213) or unchanged (195, 298) on the involved side, or the pulse might be completely absent (200). The venous pressure might either be normal (195) or high (105, 119, 200, 218) on the side of the clubbing. The blood flow after release of sympathetic tone might be abnormally high (195), abnormally low (195), or within normal limits (195) when compared with the uninvolved side. The brachial-digital pressure gradient was also correspondingly variable (195).

VIII PATHOGENESIS—THEORIES

There are many theories on the mechanism of clubbing, each with ardent advocates but none with convincing experimental support. This led West (323) in 1897 to state "Clubbing is one of those phenomena with which we are all so familiar that we appear to know more about it than we really do." Since this is as true now as it was then, a brief historical critique both of what we appear to know and of what we really do know will be presented.

A. Trophic

The view held by most physicians of the eighteenth century was that clubbing was due to emaciation, which affected the proximal more than the distal phalanges. This concept can be found in the works of Laennec (154).

B. Circulatory

No comprehensive theory was advanced, however, until the time of Pigeaux (1832) (236). He discarded the concept of emaciation since many of his patients appeared to be fairly well nourished. He believed that clubbing was due to edema and increased cellularity of the connective tissue of the finger tip, and that

3 Calorimetry All calorimetric methods for measuring peripheral blood flow are based on the principle elaborated by Stewart (292) for the hand. He showed that the number of cc of blood flowing through the hand per minute could be calculated from the number of calories eliminated per minute, divided by the difference in temperature between arterial and venous blood. He measured the number of calories eliminated by the hand in a calorimeter and took mouth temperature to be the temperature of arterial blood and average calorimeter temperature to be that of the venous blood. He assumed that all the blood flowing through the hand was cooled to the temperature of the calorimeter. The method of Hardy and Soderstrom (114) for measuring total skin blood flow calorimetrically is based on the Stewart principle and measures average blood flow per sq cm of skin. There are, however, wide variations in skin blood flow depending on vasomotor tone and the distribution of arterio-venous anastomoses. The large standard deviation from the average blood flow per sq cm in this method, therefore, makes it inapplicable for measuring blood flow in any given area such as the finger tip, although it is quite accurate for total surface blood flow.

To measure finger tip blood flow, a calorimeter was devised (195, 196) based on Stewart's method for the hand (292). It was found that Stewart's formula (292), which had been shown to be invalid for the hand (115), was applicable to the finger tip (196). This method was so simple that it could be used at the bedside, it was quantitative and technically accurate, and it could be used (196) to measure blood flow under standardized conditions, that is, after release of sympathetic tone by warming the body (235).

With this method, the blood flow per sq cm of finger tip after release of sympathetic tone, was found to be abnormally high in symmetrical clubbed fingers due to various diseases of the lungs, heart and intestine (195, 196). In a case of lung abscess in which the clubbing receded after operation, the blood flow receded to within normal limits (196). With the development of hypertrophic osteoarthropathy in these cases, however, the finger tip blood flow per sq cm of surface was found to be within the normal range of variation (196).

D Brachial-digital arterial blood pressure gradients

In all these cases (195, 196), the brachial-digital arterial pressure gradient was also determined before and after release of sympathetic tone. The brachial pressure was measured by the standard auscultatory method and the digital systolic and diastolic pressures with the Gaertner capsule (94). In symmetrical clubbing secondary to various diseases of the lungs, heart and intestines, the gradients both before (194) and especially after release of sympathetic tone were found to be less than normal (195, 196). This reduction in gradient was caused by elevated digital arterial pressure, the brachial pressure being normal. In the case of lung abscess (196), in which the clubbing receded after operation and the blood flow became normal, the digital arterial pressure and the brachial-digital pressure gradient also became normal. In three cases of hypertrophic osteoarthropathy, the digital arterial blood pressure as well as the blood flow per sq cm of finger tip was within normal limits (196).

E Toxic-mechanical

An attempt to reconcile the toxic and mechanical theories was made by incorporating both in a new theory called the toxic-mechanical. Some advocates (162-200) of this concept believed that deranged systemic (282) or impaired local (200-288) circulation produced toxins which affected the trophic nerves (192) or caused the clubbing directly. Others postulated capillary dilatation and stasis with a resultant local tissue anoxia all of which was caused by the effect of circulating toxin (38). This theory was subject to all the inconsistencies of the original toxemia theory and its modifications and also did not explain why the capillaries of the finger tips alone or of the periosteum of the bone were peculiarly susceptible to these toxins. Capillaroscopic studies in addition failed to demonstrate capillary stasis consistently (159-245-248-334).

F. Anoxic

Another theory which incorporated certain features of the toxic-mechanical theory and which has received considerable support up to the present time is the anoxic theory. According to this, capillary stasis is caused by arterial anoxemia (284), or local anoxia (47). Lebreton (162) suggested that one of the possible causes of the arterial anoxemia was pulmonary arterio-venous shunts in the involved lungs or direct shunts as in congenital heart disease. Ameuille and Perreau (5) attributed clubbing to shunts between the pulmonary artery and bronchial veins although how this produced arterial anoxemia remained unclear. The theory of arterial anoxemia broke down in cases of hereditary clubbing, unilateral clubbing and many of the pulmonary and idiopathic (46) cases in which there was no demonstrable decrease in the oxygen "saturation" of the arterial blood (162). It also failed to explain why uncomplicated methemoglobinemia or severe anemia did not produce clubbing. The theory of local anoxia failed to explain the absence of clubbing in most cases of Raynaud's disease or other diseases of the peripheral arteries. In addition these theories were subject to many of the objections to the other theories which included capillary stasis as a fundamental feature.

G Miscellaneous

Many other theories most of which were short-lived, were advanced to explain clubbing and hypertrophic osteoarthropathy. One author (49) postulated absorption of toxins from the digestive tract as the fundamental etiology. Others (131-192-231) incriminated the endocrine glands. The pituitary was one of the first to be blamed (35-106-192) because of the superficial resemblance of acromegaly to hypertrophic osteoarthropathy and because a case was reported (7) in which both diabetes insipidus and hypertrophic osteoarthropathy coexisted. The thyroid (192) was thought by some to be involved because of the rare cases of myxedema reported with clubbing. One author found hypertrophic osteoarthropathy associated with changes in mineral metabolism and tetany and therefore indicted the parathyroid glands (65). Even the gonads (192) were thought to have an influence on hypertrophic osteoarthropathy because of symptomatic changes at the time of the menstrual period (101). Advocates

these pathological changes were brought about by alterations in respiration or circulation causing a disturbance of the blood. Following this, more was done to obscure than to clarify this admirably sound concept.

C Toxic-infectious

With the advent of bacteriology and the description of hypertrophic osteoarthropathy by von Bamberger (15, 16) and by Marie (191), a toxic-infectious theory was advanced. It was believed by some (297) that the changes in the finger tips and especially in the bone were direct manifestations of chronic infection. Hypertrophic osteoarthropathy became confused with syphilitic periostitis (76, 102) and also with Poncet's so-called pseudo-tuberculous rheumatism (240). In fact, the chief infectious agent incriminated was the tubercle bacillus (3, 12, 76, 305, 306, 337). It soon became evident, however, especially when no acid-fast bacilli were found in the lesions, and when clubbing and hypertrophic osteoarthropathy were described in conditions like pulmonary neoplasm and congenital heart disease, that direct infection was neither the cause of clubbing nor of hypertrophic osteoarthropathy.

In contrast to the theory of direct infection the toxemia theory (222, 314) persisted, although under fire, for a much longer time and is even supported by some modern authors (39, 120). According to this concept, the clubbing and especially the bone lesions, are due to the effect of circulating toxins on susceptible peripheral capillaries. Why only certain varieties of toxemia, as in lung abscess or ulcerative colitis, produced clubbing, whereas others, such as in chronic rheumatoid arthritis, or chronic osteomyelitis, almost never did, remained unexplained. To explain the development of clubbing in congenital heart disease with cyanosis, Bécélère (21) suggested a hypothetical systemic toxemia resulting from the inability of the lungs to remove from the blood toxic substances produced normally by the tissues. This could be brought about by a pulmonary-systemic shunt or by impaired pulmonary function, as in various diseases of the chest. It soon became evident that this theory was inadequate to explain even ordinary varieties of clubbing, much less the hereditary or unilateral forms.

D Mechanical

The opponents of the toxemia theory supported a theory which was evolved from Pigeaux's original paper (236) and was later proposed as an alternative explanation for the mechanism of clubbing and hypertrophic osteoarthropathy by von Bamberger (15, 16). This became known as the mechanical theory (28, 36, 81, 135, 314), according to which, clubbing was believed to be due to capillary stasis because of back pressure. The cases of unilateral clubbing with venous obstruction and cases of bilateral (48) and unilateral (280) clubbing in which release of venous obstruction caused partial recession of the clubbing were cited. Ordinary symmetrical clubbing was attributed to back pressure from the heart and lungs. Why patients with heart failure rarely developed clubbing remained unexplained. In ordinary symmetrical clubbing, moreover, stasis was not substantiated by actual pressure measurements.

passive hyperemia Ogle (218), Obermayer (216) and Achard (2) also postulated overnutrition, but because of passive hyperemia Ferrio (83) and also Szydlowski (298) thought that the overnutrition of the tissue was due to vasomotor changes (dilatation) affecting chiefly the arteries and capillaries Von Czyhlarz (63, 64) believed that the overnutrition was due to active hyperemia because some of his cases of subacute bacterial endocarditis with clubbing happened also to have aortic insufficiency which was accompanied by peripheral vasodilatation Walters (317) mentioned active hyperemia as a possible cause of clubbing only to dismiss it It is apparent hence, that the concept of overnutrition of tissue was arrived at by several observers and that some thought increased blood flow to be responsible for this Although these opinions were based on erroneous premises and therefore usually dismissed, they nevertheless were never disproved Recent evidence from clinical observation and experiment (196-199) has re-emphasized the importance of increased peripheral blood flow in the development of clubbed fingers and hypertrophic osteoarthropathy

Any new theory of the mechanism of clubbing and hypertrophic osteoarthropathy would have to incorporate all the facts presented here, as well as any new ones discovered in the course of clinical investigation or animal experimentation In my opinion, increased peripheral blood flow would have to form a cornerstone of the new theory

IX SUMMARY

1 Symmetrical clubbing of the fingers and toes may be acquired in the course of various systemic diseases or may be hereditary Unilateral and undigital clubbing apparently occur in association with vascular and vasomotor diseases of the corresponding extremity or finger Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of the extremities and may develop in any condition capable of producing clubbing

2 Characteristic clinical and roentgenological changes occur in clubbing and hypertrophic osteoarthropathy

3 Clubbing and hypertrophic osteoarthropathy are seen pathologically to consist chiefly of tissue hypertrophy and hyperplasia In the original bone, however, osteoclasia and bone resorption may be stimulated

4 Hypertrophic osteoarthropathy was produced experimentally in the dog by anastomosis of the pulmonary artery to the left auricle The most significant circulatory change found was an increase in systemic cardiac output

5 Clinical physiological observations have demonstrated in simple acquired symmetrical clubbing an increase in blood flow per unit of tissue caused chiefly by an increased digital arterial pressure In hereditary clubbing and in hypertrophic osteoarthropathy these changes in digital arterial pressure and blood flow were absent In unilateral clubbing they were variable

6 Previous theories on the pathogenesis of clubbing are reviewed historically and discussed critically

7 It is believed that increased peripheral blood flow will form a cornerstone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy

of the nervous theory (34, 45, 127, 262) believed that the effect of nerve lesions, especially those of the autonomic nervous system, on vasomotor tone was responsible for clubbing and the bone lesions. They cited the cases of syringomyelia (33), some of the unilateral cases with nerve lesions (26, 110, 186, 193, 203), and experimental as well as clinical observations demonstrating the relationship between nerve injury and tissue hypertrophy (130, 166, 298). Pathological studies, however, failed to confirm the presence of nerve lesions in most of the cases of clubbing (44) or of hypertrophic osteoarthropathy (300). Another theory proposed was that of lymph stasis (78). The author here cited cases of bone changes secondary to lymphangitis of the lower extremities. Lymphangitis, however, may produce an inflammatory periostitis (54), which must be carefully distinguished from hypertrophic osteoarthropathy. Moreover, clubbing and associated bone changes are absent in most cases of lymph stasis, and there is no evidence of such stasis in most of the varieties of clubbing, with the possible exception of unilateral clubbing. One author (242) thought hereditary clubbing to be due to changes in blood volume, but this also has not been confirmed. Among the more fantastic theories proposed and completely unsupported by evidence is that of increased intracranial pressure (278). Another is the theory that clubbing is due to excessive cooling of the finger tips (149). One author postulated a vitamin deficiency (61) and another the liberation of nitrogen gas in the periosteum (331) as the cause of hypertrophic osteoarthropathy. Most of these theories have been abandoned as accumulated evidence either failed to support or directly disproved them.

H Eclectic

It was evident to some observers (129, 170, 299) that no one of the proposed theories was reconcilable with all of the known facts. Of these workers, some attempted to effect a compromise by postulating different mechanisms for different kinds of cases (16, 34, 38, 138, 264). Thus, in any given case, the underlying cause might be either toxemia, anoxemia, stasis, nerve lesions, etc., or any combination of these factors. They believed that all these factors might produce similar local capillary effects, such as stasis or impairment of permeability and that this in turn was the cause of the clubbing. This was again controverted by the absence of demonstrable capillary stasis in many clubbed fingers examined with the capillaroscope, and it did not satisfy the desire to explain a single phenomenon like clubbing and hypertrophic osteoarthropathy by a single mechanism. Those who held fast to that desire simply stated that the mechanism of clubbing must be considered to be unknown (324).

I Future

Out of this welter of hypothesis and theory appeared certain concepts which were never controverted by facts. The concept that clubbing and hypertrophic osteoarthropathy were essentially a hypertrophy and hyperplasia which might or might not be accompanied by local edema remained in accord with the evidence. Von Bamberger (15) thought that this hyperplasia was due to an over-nutrition of the tissues by the blood, which could occur in both active and

passive hyperemia Ogle (218), Obermayer (216), and Achard (2), also postulated overnutrition but because of passive hyperemia Ferno (83) and also Szydlowski (298) thought that the overnutrition of the tissue was due to vasomotor changes (dilatation) affecting chiefly the arteries and capillaries Von Czyhlarz (63, 64) believed that the overnutrition was due to active hyperemia, because some of his cases of subacute bacterial endocarditis with clubbing happened also to have aortic insufficiency, which was accompanied by peripheral vasodilatation Walters (317) mentioned active hyperemia as a possible cause of clubbing only to dismiss it It is apparent hence, that the concept of overnutrition of tissue was arrived at by several observers and that some thought increased blood flow to be responsible for this Although these opinions were based on erroneous premises and therefore usually dismissed, they nevertheless were never disproved Recent evidence from clinical observation and experiment (196, 199) has reemphasized the importance of increased peripheral blood flow in the development of clubbed fingers and hypertrophic osteoarthropathy

Any new theory of the mechanism of clubbing and hypertrophic osteoarthropathy would have to incorporate all the facts presented here, as well as any new ones discovered in the course of clinical investigation or animal experimentation In my opinion, increased peripheral blood flow would have to form a cornerstone of the new theory

IX SUMMARY

1 Symmetrical clubbing of the fingers and toes may be acquired in the course of various systemic diseases or may be hereditary Unilateral and undigital clubbing apparently occur in association with vascular and vasomotor diseases of the corresponding extremity or finger Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of the extremities and may develop in any condition capable of producing clubbing

2 Characteristic clinical and roentgenological changes occur in clubbing and hypertrophic osteoarthropathy

3 Clubbing and hypertrophic osteoarthropathy are seen pathologically to consist chiefly of tissue hypertrophy and hyperplasia In the original bone, however, osteoclasia and bone resorption may be stimulated

4 Hypertrophic osteoarthropathy was produced experimentally in the dog by anastomosis of the pulmonary artery to the left auricle The most significant circulatory change found was an increase in systemic cardiac output

5 Clinical physiological observations have demonstrated in simple acquired symmetrical clubbing an increase in blood flow per unit of tissue caused chiefly by an increased digital arterial pressure In hereditary clubbing and in hypertrophic osteoarthropathy these changes in digital arterial pressure and blood flow were absent In unilateral clubbing they were variable

6 Previous theories on the pathogenesis of clubbing are reviewed historically and discussed critically

7 It is believed that increased peripheral blood flow will form a corner-stone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy

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RECENT ADVANCES IN THE EPIDEMIOLOGY OF PNEUMOCOCCAL INFECTIONS*

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The most accurate and reliable studies on the epidemiology of pneumonia have been made since the introduction of the classification of pneumococci into specific types by the work of Neufeld and Haendel (1), Lister (2), Dochez and Gillespie (3) and, more recently, by Cooper (4). A considerable number of significant observations, however, had previously been made concerning the spread of pneumonia both before and after the discovery of the pneumococcus. Some of the highlights of these early observations may be mentioned briefly.

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RECENT ADVANCES IN THE EPIDEMIOLOGY OF PNEUMOCOCCAL INFECTIONS*

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The most accurate and reliable studies on the epidemiology of pneumonia have been made since the introduction of the classification of pneumococci into specific types by the work of Neufeld and Haendel (1), Lister (2), Dochez and Gillespie (3) and, more recently, by Cooper (4). A considerable number of significant observations, however, had previously been made concerning the spread of pneumonia both before and after the discovery of the pneumococcus. Some of the highlights of these early observations may be mentioned briefly.

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Some of the more precise studies on the rôle of air and dust in the spread of pneumonia that were carried out in later years with the aid of typing were anticipated by a number of earlier workers in addition to Netter (13). Emmerich (15) recovered pneumococci from the floor filth in a prison which was notorious for breeding pneumonia over a period of 25 years. Pawlowsky (16) isolated, on solid media, pneumococcus-like organisms from a number of rooms. Netter (14), Emmerich (15), Germano (17), Bordoni-Uffreduzzi (18) and Wood (19), among others, demonstrated the resistance of pneumococci to drying. Some of these studies were made with dust, sputum and linens. Washbourn (20) was able to recover pneumococci by mouse inoculation of the dust from a ward in which pneumonia patients were nursed but not from other wards nor from the dust of the hospital entrance hall, the laboratory and the street. The resistance of pneumococci to drying at different temperatures and the effect of daylight were recently restudied by Stillman (21, 22).

Epidemics involving multiple cases in families or in institutions, in which direct contagion was traced, have been described either separately or in connection with outbreaks in small communities. In some of them, the pneumococcus was identified by culture or mouse inoculation at least in a number of cases (23-24), while others lacked bacteriologic data (25-28). Azéma (25) related a number of instances including some from his own experience, of direct contagion among persons occupying the same room, of spread not only within the same family but to contacts outside of the family, and of pneumonia contracted by a physician from his patient and transmitted in turn, to members of his own household. Outbreaks of focal pneumococcal infections have been recorded both in association with pneumonia (29, 30) and independently (31). Axenfeld (31) described an epidemic of pneumococcal conjunctivitis in children, many of whom had colds at the time, and Antoniu (29) and Rey (30) observed many cases of otitis media, accompanying pneumonia in some instances, and identified the pneumococci in the purulent aural discharge.

Pneumonia acquired in foundling homes was recognized as an important cause of the high death rates in infant asylums. Jacobi (32), in 1872, listed this disease as one of the chief causes of death during their stay in asylums, of babies who were healthy on arrival.

In the pneumonias that occurred during the construction of the Panama Canal (33-34) and in the South African mining camps (34-35) two important factors have been stressed, namely overcrowding and the high attack rates in new laborers within a short time of their arrival. The factor of direct contagion was not considered important by Maynard (35) but it was clearly recognized at Panama, where the epidemic spread of the disease was stopped as soon as the laborers were permitted to build their own huts in the neighboring hills or to live with their families in the cities (34).

BACTERIOLOGIC METHODS APPLIED TO THE EPIDEMIOLOGY OF PNEUMONIA

It is well recognized that, in pneumococcal infections as in other diseases, the reliability and the efficiency of the laboratory methods used in isolating and identifying the pathogenic strains of organisms involved are of paramount im-

EARLY REPORTS DEALING WITH THE CONTAGIOUSNESS OF PNEUMONIA

Numerous epidemics of disease considered to be pneumonia were described prior to the discovery of the pneumococcus. Most of these have been reviewed by Hirsch (5), and many were reviewed by Woods (6) and by Gundel (6a). In the American literature, Wells (7) presented an annotated chronology of 222 epidemics in all parts of the world from 1440 to 1880. Most of those recorded occurred in Italy, France and Switzerland, and they included a great variety of special classes or groups of individuals. For example, some involved only children, others only natives, while a number were limited to schools or occurred on board ships. From the description of some of these epidemics, there is reason to believe that many which are included as examples of pneumonia in reality constitute a variety of diseases. Also, in many of the epidemics where it may be presumed that pneumonias did occur, they were probably secondary to other diseases and very likely were not caused by the pneumococcus. Certainly the most extensive outbreaks which assumed pandemic proportions were associated with other infections, notably influenza. As Heffron (8) has pointed out, it seems improbable that any extensive outbreaks of lobar pneumonia, that is, of pneumococcus pneumonia, have ever occurred. While pneumonia may increase in prevalence in wide areas and even in large portions of a whole country during some seasons, it is the localized outbreaks which have been the most impressive and have comprised the bulk of the literature.

The pneumococcus was first isolated from the saliva of persons without pneumonia and was later identified as the causative organism of this disease (9). This naturally led most of the earlier investigators to consider pneumonia to be an autogenous infection (10) and, while epidemic outbreaks were recognized, their occurrence was often ascribed to environmental factors or to factors which depress the resistance of the individuals. Similar opinions have been current until very recently and are probably still held by a number of clinicians (11). The ideas concerning the epidemiology and contagiousness of pneumonia during the early history of the pneumococcus were reviewed by Mendelsohn (12). As early as 1888, however, Netter (13, 14) brought forth evidence, mostly on clinical grounds, for the contagiousness of pneumonia. He recognized many of the important epidemiological features of the disease, as well as the part played by the pneumococcus in its contagion. He described family outbreaks in which both pneumonia and other focal pneumococcal infections played a part, even in the same household. He was able to trace cases to direct contact with other cases, although sometimes this contact was very brief. Two possible sources of contagion were considered: one was healthy human carriers acting as vectors, and the other was inanimate objects, such as clothing or furniture. Instances of hospital infections, both from active cases and from convalescents, are cited. While he considered that the disease could be contracted at a distance, presumably through organisms suspended in the atmosphere, he found that this did not take place at any greater distance than the space of three beds. He also found that pneumococci survived in dried sputum for many months, and he recovered them from the dust of a hospital room.

siderably and that their significance in human infections does not necessarily parallel their virulence for mice (S2). When multiple types are simultaneously inoculated into a culture medium or into an animal, the yield of each will depend on the numbers of each type that are inoculated, on the facility with which each will grow in the given medium in the case of the cultures, and on the comparative virulence of the strains in the case of animal inoculation. This "bacterial antagonism" between the different types (S3, S4) can usually be overcome, and all the different types eventually can be isolated and identified by "blocking" the known types by the simultaneous inoculation of homologous immune serum. Multiple types that are not readily picked up by the ordinary methods may thus become apparent (S5-S7). With the use of the Neufeld method, this "blocking" procedure is rarely necessary, since with the direct typing all the types can usually be identified from the same medium. The procedure may still be employed if it is desired to obtain the various organisms in pure culture.

Before the Neufeld method of typing came into general use, it was necessary to inoculate the suspected materials into mice either directly or after preliminary incubation in suitable fluid media as already indicated. The peritoneal exudate of the mouse or a culture of its heart's blood, or both, were typed after the animal died or was sacrificed. Usually subcultures were made on blood agar plates, individual typical colonies were picked and subcultured in fluid media and then typed after they were identified by morphology and bile solubility. For the most part, the typing was carried out by macroscopic agglutination, but sometimes it was done microscopically (S8). The slide agglutination could also be applied to peritoneal exudates withdrawn by capillary pipette without sacrificing the mouse (S8). At present, the "Quellung" reaction for typing may be applied at any stage of these procedures. Even individual colonies may be emulsified and typed directly in this manner. If one is interested in identifying a single type only the homologous serum need be used. In any case, after one type is determined further serums need ordinarily be used only if organisms are seen which do not show the typical reaction with serum of that type. The characteristic morphology and swelling, when they are obtained only with serum of a single type, may be considered as essentially confirming both species and type. If capsular swelling occurs with antiserums of more than one type it may be necessary, in order to eliminate possible cross reactions to pick characteristic colonies and then subculture and identify them.

Obviously many of these procedures may be eliminated because they are not likely to yield enough additional information to warrant the time, materials and effort. On the other hand, if too many of these procedures are eliminated, a large number of strains may readily be missed. The detection of variants of type-specific pneumococci (S9-99) which have lost their virulence, type-specificity and the smooth character of colony growth on suitable solid media may require special care. At times, it is possible to cause these "rough" strains to revert to their smooth character and original mouse virulence by animal passage, and the organisms then regain their type-specific character. Since such rough strains have been recovered from animals (92), from human carriers (79) and

portance in the interpretation of the results of epidemiologic studies¹ The fact that pneumococci can be classified accurately into specific types which vary considerably in their pathogenicity has been of great help, not only in identifying the causative agent in patients with manifest infection, but also in tracing the spread of these organisms among the healthy and the infected

In addition to the obvious necessity of using proper media, which usually means nutrient broths to which serum or defibrinated blood is added (36), three special aids have been of particular importance in pneumococcus epidemiology They are the use of mouse inoculation (36), the extension of the classification of pneumococci to include the strains which were formerly classified as Group IV (4) and the direct typing by use of the specific Quellung reaction of Neufeld (37-43)

The importance of mouse inoculation as a means of isolating pneumococci, when present in small numbers and particularly when mixed with other organisms of the common respiratory flora, is well recognized In general, the results of mouse inoculation have been highly reliable (44) and usually, but not always (45), there is a considerable number of instances in which types revealed by the mouse inoculation are missed by cultural methods alone (46-48)

By means of the Cooper types (4), it is usually possible to classify all but a minor residue of the pneumococci isolated from all sources (4, 8, 49-54), but in some studies on normals there may still be a high residue of untyped pneumococci (55, 56)

Most of the earlier epidemiologic studies revolved about Types I and II pneumococci as the important types in adult lobar pneumonia, and Type III as the commonest type in healthy carriers (36, 57-64) Since some of the newer types are more important than any of these three types in the infections of infants and children, the study of outbreaks among them has been made possible by this extended classification (54, 65-68) Further refinements have recently been described which concern some additional new types and other types related to those already described (69-76) They are probably not of very great importance from a general epidemiological point of view, but they may be important in some outbreaks

The Neufeld method of typing has made possible the identification of pneumococcus types directly from sputum or other infected materials and from cultures even when the organisms are present in relatively small numbers and in the presence of numerous other bacteria (37-43) It has been of the greatest value in recent epidemiological studies (45, 48, 56, 67, 68, 77-81) In most instances, multiple pneumococcus types from the same source, such as sputum, nose or throat cultures or peritoneal exudates of mice inoculated with such materials, can all be accurately identified before they are isolated in pure culture

With respect to mixed cultures of pneumococcus types, it is recognized that these multiple types may be present in different numbers in the same individual, that the pathogenicity of the individual types for human beings may vary con-

¹ The various methods of isolating and typing pneumococci are reviewed in pp 614 to 645 of Hefron's book (8)

pharynx and over both tonsillar fossae. It is preferable to have the swab wrapped on the bent end of a pliable wire which is passed behind the soft palate to one side of the uvula and rubbed against the posterior nasopharynx. The swab is then streaked across a blood agar plate and placed into broth containing serum or defibrinated blood (preferably of a rabbit). The latter is incubated until any blood cells present have settled and a diffuse hazy growth appears in the medium. This usually requires from 4 to 8 hours. The culture may then be examined by the Neufeld method but unless there are adequate numbers of pneumococci it usually is necessary to inoculate a mouse with about 0.5 ml. of this growth and then to examine the peritoneal exudate etc. as in the case of sputum.

Nasal cultures are best made by using a cotton swab moistened in saline (or broth, which is even better) and rotating it in both nares. The swab is then treated in the same manner as the pharyngeal swab. A more satisfactory method whenever applicable is that used by Neufeld (103-104). This involves flushing each nostril with saline (or broth) and collecting it as it comes out of the opposite nostril. Such material from persons with nasopharyngeal infections can often be examined satisfactorily by direct Neufeld typing or it is streaked on a blood agar plate and inoculated into a mouse and then treated the same as sputum. It is most important to include nasal cultures when dealing with infants and young children (56-62, 67).

The amount of effort expended on any given specimen will depend to a large extent on the importance attached to the results. For example, if materials are being collected merely to determine the incidence of carriers the individual results are not so important and the simpler methods are employed. On the other hand, in tracing the source of a single infection or of an outbreak it may be advisable to use many more procedures and these may profitably be repeated before any suspect can with assurance be eliminated as a source of contagion. Furthermore, if it is desired merely to establish the presence or absence of pneumococci of a given type subsequent procedures can be omitted as soon as that type has been identified. In many instances only the original material or the first culture on a fluid or solid medium will provide the answer.

The extensive use of sulfonamide drugs has raised new problems which may have a bearing on the epidemiology of pneumonia. Fewer positive cultures are obtained in patients treated with sulfapyridine or sulfathiazole than in those who do not receive such treatment (105). Pneumococci of the same or of different types have been shown to vary in their susceptibility to the action of sulfonamide drugs both *in vitro* and in therapeutic experiments in animals (106-112). Resistance or "fastness" to these drugs may be induced in previously susceptible strains *in vitro* (112-113) and similar changes apparently occur in human infections as well as in experimental infections in animals when sulfonamide therapy is used (110, 112-114-117). Drug fastness however in no way alters the type specificity, morphology or virulence of the pneumococci (115, 117). Fastness to one effective sulfonamide drug is usually associated with resistance to other sulfonamide derivatives as well (112-118). The frequency with which strains

from patients with pneumonia (96, 99), they may play some rôle, as yet undetermined, in the epidemiology of pneumonia. It is not known whether conversion of rough strains to smooth ones of types other than those from which they are derived occurs spontaneously in the living host the same as it does in experimental animals (90, 97, 98). In fact, it is not even known whether rough variants in human beings ever become smooth in their original host, although in some instances nontype-specific strains have acquired specific type characteristics upon mouse passage after their original isolation (79, 99).

Other factors, in addition to the cultural methods, may be of equal or even greater importance. The sources of the materials obtained for culture, the care with which these are collected and handled, whether from a single or from multiple sources and the number of times such cultures are taken—all these factors influence the yield of positive cultures and the number of types obtained from any given individual or group (56, 60, 79, 87).

In the culture of materials from air, dust, skin and fomites, solid media (blood agar plates) are sometimes seeded directly. Methods similar to those used in isolating hemolytic streptococci from corresponding sources may be used for collecting the materials (100, 101). Swabs moistened with saline or, better still, with broth, if feasible, are rubbed on the materials in question and then streaked on the surface of the media. Further cultures in suitable broth medium and mouse inoculation of some of this medium, either with or without preliminary incubation, are highly advantageous (57). The scrub water used for washing the hands may be employed for making quantitative cultures from the surface of the skin (102).

For the culture of materials from cases or carriers, one cannot be dogmatic in recommending the best procedures to follow in order to obtain the maximum yield of positive pneumococcus cultures and the largest number of types from any given specimen with the minimum expenditure of time, materials and effort. Much will depend on the particular materials being studied. From personal experience and from the results reported by many other workers, the following procedures are recommended.

For sputum, nasal discharge or other purulent materials (1) Direct examination by the Neufeld method, and a Gram stain to serve as a rough guide to the morphology and general bacterial flora. (2) Direct inoculation of blood- (or serum-) broth and blood agar plate, and examination of the resulting culture or of characteristic colonies from the surface of the blood agar plate by Gram's stain and the Neufeld method. (3) Mouse inoculation of the material, intraperitoneally, and examination of the exudate withdrawn after an interval of 3 to 8 hours, depending on the number of organisms seen in the original preparations. (4) Further procedures, such as examination of the peritoneal exudate and heart's blood of the dead or sacrificed mouse and of characteristic individual colonies from blood agar plates seeded with these materials, are usually only confirmatory and rarely yield additional data of value. In fact, even procedures (2) and (3) usually prove redundant.

For pharyngeal cultures. A swab is rubbed thoroughly over the posterior

infecting organisms into a terminal bronchus and to insure their remaining in place for some time by suspending them in a thick starch paste. A preliminary injection of morphine sufficient to reduce the body temperature and application of cocaine to the larynx have also been used. These procedures presumably inhibit some of the reflexes ordinarily active in eliminating bacteria from the respiratory tract (135). Likewise, alcoholic intoxication and anesthesia seem to alter the local reaction of the tissues of the mouse (136-138) and the rabbit (139, 140) and permit invasion of the tissues. Even the immune mechanism may be inhibited under these conditions and organisms may remain viable *in situ* long enough to multiply, after which they may spread and invade.

Active immunization by means of vaccines injected intravenously, subcutaneously or intraperitoneally, or passive immunity with antipneumococcus serum, usually prevents infection by inhalation or by the intranasal or intrabronchial routes in mice, rabbits and monkeys (127, 133, 134, 141). The greatest protection from active immunization is against pneumococci of the homologous type, but some resistance to infection with heterologous types also occurs. Specific antisera, however, protect only against the homologous type (127). In partially immunized mice, localization of infection may take place in the lungs (127, 137), but the same may not be true of rabbits (138, 139). Normal or partially immune animals which survive infection by the respiratory route, or which fail to become infected after inhalation or after nasal instillation of living pneumococci, develop resistance to further infection either with or without the development of transferable antibodies (126, 128, 133, 142-146). Mice and guinea pigs which survive spraying or intranasal infection may become carriers (103, 104, 127, 132, 134, 147). Some carrier mice, however, may succumb to septicemia as long as 15 days after infection (127). Some degree of resistance may be acquired by repeated inhalation or instillation of dead pneumococci (126, 148).

Pneumococcus Carriers among Healthy Animals Pneumococci have been cultivated from the upper respiratory tract, and occasionally from the lungs, of apparently healthy animals of a variety of species, including guinea pigs, rabbits, horses, calves, dogs, monkeys and the brown bear (20, 103, 104, 147, 149-160). In some of these animals there may be an associated focal infection, such as sinusitis or rhinitis in the guinea pig (103, 147) and lung abscess in the horse (153). In guinea pigs they are found most frequently in the presence of upper respiratory infections (104). The carrier rate usually rises during epidemics and is highest after the epidemic subsides.

Most of the pneumococci found in normal animals have not been identified serologically, and those that were fell into Group IV (157-161). In the course of one outbreak of Type II pneumonia in monkeys the exposed animals which did not have manifest infections were found to harbor the same type (158). Type XIX pneumococcus was found to be the most prevalent type in both healthy and infected guinea pigs of various laboratories and dealers in Berlin and elsewhere in Germany. For this species, Type XIX was found to be more virulent than Type I pneumococci. Following the simultaneous intranasal

encountered clinically are found to be resistant, when moderate numbers are subjected to therapeutic concentrations of sulfonamide drugs, is probably not very great (105, 110, 112, 119, 120) It is probably not of great significance at present except as an aid in explaining certain clinical failures from chemotherapy (105, 110, 112, 120) The possibility of epidemics of infections with sulfonamide-fast strains in the future must be considered (121) A number of methods have been proposed for the recognition of sulfonamide-fast strains (110, 112, 119, 122) These usually depend on a comparison of the growth of the organism on suitable media, with and without the bacteriostatic drug The procedure may sometimes be hastened by the use of mice (120)

PNEUMOCOCCAL INFECTIONS IN ANIMALS

Most of the literature on pneumococcal infections in animals is concerned with studies of experimental infections carried out for various purposes² In this review, we need consider only such aspects of these studies as concern the attempts to produce infection by what might be considered as "natural" routes, namely, by inhalation or by intranasal administration Some of the more relevant recent observations concerning the occurrence of pneumococcus carriers and of spontaneous infections and epidemics in animals will also be summarized

Experimental Infection of Animals by "Natural" Routes Natural infection, occurring simply as a result of inhaling pneumococci, is probably quite rare in the common experimental animals Mice, which are highly susceptible to infection by the intraperitoneal or other parenteral routes, usually resist infection by inhalation of pneumococci in a spray (123) Virulent pneumococci may disappear from the respiratory tract of mice even when they are sprayed with infected bloody sputum from pneumonia patients (124) Most of the inspired organisms probably fail to get below the larynx Presumably they are filtered out chiefly in the upper respiratory tract, and those that do get down lower are eliminated in various ways (125) Stillman (123) considered the normal lung of the mouse to be an unfavorable site for establishing infection Some organisms, however, probably do gain access to body tissues following inhalation and, although they may not multiply, they may still induce an immune response, especially after repeated inhalations (126)

Pneumococci vary in their ability to produce infection by inhalation This may depend in part on the type and virulence of the strain and on the number of bacteria inspired, and the rabbit may be more susceptible to infection in this manner than is the mouse (127-131) Different strains also vary in their ability to produce infection by the intranasal route (131-134) Virulence for mice, as measured by infection either through inhalation or by intranasal instillation, is largely independent of intraperitoneal virulence (130-132, 134)

Presumably other factors in the lung that are not clearly understood are also necessary in order to establish infection (123) For the production of pneumococcus lobar pneumonia in the dog (135) it seems necessary to place the

² The literature on experimental infections is summarized on pp 204 to 232 of Hefron's book (8) and also in Chapter VI of White's book (9)

type was recovered from many healthy guinea pigs. In one small epidemic in that city the organisms were mucoid pneumococci that could not be identified serologically (104). Branch (167) found a pneumococcus of low virulence that was not Type I, II or III in an outbreak among his guinea pigs. Several strains that he tested were all related by their agglutination reactions and probably were of the same type. The organism recovered from a spontaneous infection in a rabbit was likewise a Group IV strain (171). Such strains have been reported from most epidemics in which typing was attempted (157, 161, 176).

In one of the epidemics among monkeys the Type II pneumococcus was found in all infected and contact animals (158). In another outbreak in monkeys (170) Group IV pneumococci were cultured from the lesions of infected animals and shown to belong to two serological groups. The animals having the related strains were in contact with each other and became ill at about the same time. In this epidemic, only the animals of two lots were involved and those of a third lot escaped infection completely. In the latter the animals were kept separated with only two in a cage whereas the other two lots had been kept under crowded conditions.

Vaccination was employed in several of the outbreaks. New infections did not occur after the vaccination (158, 165, 166). In one outbreak vaccination was without effect when care was not taken in the choice of a strain for the vaccine. When the infections occurred during the following year however the epizootic was promptly stopped by vaccination with a strain isolated from one of the sick animals (165). Among guinea pigs it may be necessary to exclude all animals having nasal infections as well as all carriers and in addition to vaccinate the entire stock in order to avoid epidemics (104). Combined intraperitoneal and intranasal serum administration was found necessary in order to eliminate the carrier state in guinea pigs (177). Ethyl hydrocupreine had no effect in the treatment of the infection (164) or on the carrier state (177).

While spontaneous epidemics in animals are usually difficult to reproduce experimentally and most attempts have failed (163, 167) it has been found possible to infect normal noncarrier mice and guinea pigs by exposure to infected guinea pigs. Even carrier animals can transmit the infection (147). Mice infected intranasally can transmit the infection by contact with normal mice (132) but it has not been spread from mice infected by inhalation (178). Hemolytic streptococci and Friedländer's bacillus infection of mice likewise failed to spread by contact from animals infected by inhalation (179).

OCURRENCE OF TYPE-SPECIFIC PNEUMOCOCCI IN PNEUMONIA AND IN HEALTHY CARRIERS

It has already been noted that the pneumococcus was first isolated from the saliva of normal persons. The occurrence of healthy carriers of pneumococci therefore has long been appreciated. As early as 1905 Park and Williams (180) pointed out that pneumococci obtained from patients with pneumonia are predominantly typical strains whereas those isolated from healthy individuals include a higher percentage of 'atypical' strains. During the winter months

infections with equal numbers of organisms of these two types, the Type XIX gave rise to infection and the organism persisted after the infection subsided, while the Type I organisms disappeared rapidly. This is the opposite of what happens in mice under the same conditions, that is, the Type I organisms give rise to the infection and rapidly displace the Type XIX organisms (104). A large proportion of the stock guinea pigs may be carriers during an outbreak (157, 158) and the high percentage of pneumococcus carriers may persist in the colony for several months after the epidemic subsides (157). In normal monkeys, examined shortly after they were received from the dealer, many strains of human pathogenic bacteria are found, including Types III, IV, V, VII, VIII, XIX and XXII pneumococci (149). Some avirulent strains have also been found (160).

Spontaneous Outbreaks among Animals Most of the early reports of spontaneous pneumococcal infections in animals were reviewed by Smith in 1913 (162) and by Meyer in 1928 (163). Outbreaks have most frequently been noted among guinea pigs (104, 147, 153, 155-159, 161-169). New arrivals in the stock have been particularly affected in some outbreaks (159, 164). Newborn animals may acquire upper respiratory infections early, and then die of pneumonia 2 or 3 months later (104). Newborn calves are particularly susceptible (154). Some of the outbreaks have involved mostly adult guinea pigs (165, 166), with a high rate of abortion and a high fatality rate among the pregnant females (104, 166). Epidemics have also been observed among monkeys (158, 170). Among the latter animals, the infection usually is associated with typical lobar pneumonia, frequently bilateral, while among guinea pigs there is a primary septicemia with focal infections, such as pericarditis and purulent pleurisy and some atypical pulmonary lesions. Spontaneous infection in a rabbit, presumably air borne, has also been reported (171).

The factors most frequently considered to predispose to the epidemic infections in animals are crowding (163, 170), especially in dark and dirty cages, some indefinite lowering of resistance of individual animals, particularly through injury or experimental procedures (153-157, 159, 163, 164, 172-175) or through some supposed dietary defect (159, 162, 165, 172, 176), pregnancy (104, 166), other superimposed infections, particularly with *Pasteurella* (157, 162, 163, 169), and season (162, 165, 167), which has been related to diet and to chilling (155, 156, 159)³. Some of the epidemics have subsided during the summer months, only to recur in the fall (159, 162, 165-167). In one epidemic, pneumococci were cultured from the animal feed (hay) and were also recovered from blood agar plates exposed to the air and dust of the cages housing the infected animals (157).

The pneumococci recovered from a series of outbreaks among guinea pigs in various divisions of the Robert Koch Institute and in the Berlin department of health laboratory were all identified as Type XIX and, as already noted, this

³ Wooley and Sebrell (332) have recently shown that a deficiency of riboflavin or thiamin increases the susceptibility of mice to a fatal experimental infection with pneumococcus Type I by the intranasal route.

type was recovered from many healthy guinea pigs. In one small epidemic in that city the organisms were mucoid pneumococci that could not be identified serologically (104). Branch (167) found a pneumococcus of low virulence that was not Type I, II or III in an outbreak among his guinea pigs. Several strains that he tested were all related by their agglutination reactions and probably were of the same type. The organism recovered from a spontaneous infection in a rabbit was likewise a Group IV strain (171). Such strains have been reported from most epidemics in which typing was attempted (157, 161, 176).

In one of the epidemics among monkeys the Type II pneumococcus was found in all infected and contact animals (158). In another outbreak in monkeys (170), Group IV pneumococci were cultured from the lesions of infected animals and shown to belong to two serological groups. The animals having the related strains were in contact with each other and became ill at about the same time. In this epidemic, only the animals of two lots were involved and those of a third lot escaped infection completely. In the latter, the animals were kept separated, with only two in a cage, whereas the other two lots had been kept under crowded conditions.

Vaccination was employed in several of the outbreaks. New infections did not occur after the vaccination (158, 165, 166). In one outbreak, vaccination was without effect when care was not taken in the choice of a strain for the vaccine. When the infections occurred during the following year, however, the epizootic was promptly stopped by vaccination with a strain isolated from one of the sick animals (165). Among guinea pigs, it may be necessary to exclude all animals having nasal infections as well as all carriers and, in addition, to vaccinate the entire stock in order to avoid epidemics (104). Combined intraperitoneal and intranasal serum administration was found necessary in order to eliminate the carrier state in guinea pigs (177). Ethyl hydrocupreine had no effect in the treatment of the infection (164) or on the carrier state (177).

While spontaneous epidemics in animals are usually difficult to reproduce experimentally, and most attempts have failed (163, 167), it has been found possible to infect normal noncarrier mice and guinea pigs by exposure to infected guinea pigs. Even carrier animals can transmit the infection (147). Mice infected intranasally can transmit the infection by contact with normal mice (132), but it has not been spread from mice infected by inhalation (178). Hemolytic streptococci and Friedländer's bacillus infection of mice likewise failed to spread by contact from animals infected by inhalation (179).

OCURRENCE OF TYPE-SPECIFIC PNEUMOCOCCI IN PNEUMONIA AND IN HEALTHY CARRIERS

It has already been noted that the pneumococcus was first isolated from the saliva of normal persons. The occurrence of healthy carriers of pneumococci, therefore, has long been appreciated. As early as 1905, Park and Williams (180) pointed out that pneumococci obtained from patients with pneumonia are predominantly "typical" strains, whereas those isolated from healthy individuals include a higher percentage of 'atypical' strains. During the winter months

they found typical pneumococci in the throat secretions of a large percentage of healthy persons, both in the city and in the country. They felt that pneumonia should be considered contagious and that steps should be taken to control its spread through expectoration. Longcope and Fox (181) found pneumococci irregularly in 40 to 50 per cent of normal persons and recognized that some individuals may be persistent carriers. Hiss (182) noted a similar frequency of healthy carriers, but found the incidence to be higher when repeated cultures were made. He felt that all persons probably carry pneumococci during the winter months, and considered that these pneumococci may be related to some of the common colds. Goeters (183a) cultured pneumococci from 82, or 46 per cent, of 202 normal lungs. All of these pneumococci were found to be Group "X", and in 57 of the lungs these pneumococci were the only or predominant organisms. Norris and Pappenheimer (183b) found pneumococci and streptococci in both normal and diseased lungs in practically all persons at autopsy. They did not feel, however, that these organisms were necessarily present in the lung during life.

Soon after the introduction of Dochez and Gillespie's (3) classification of pneumococci, epidemiologic studies showed that Type I and Type II organisms were intimately associated with primary lobar pneumonia and were found almost exclusively in relation to this disease. The pneumococci isolated from healthy carriers were usually found to be either Type III or unclassified strains, which were included in Type IV or what should preferably be called Group IV (Group "X" in the German literature). Types I and II pneumococci were found in healthy carriers only when they had been in intimate contact with cases of lobar pneumonia (46, 57, 58, 69, 184-194). While pneumococci other than Types I and II were also found to give rise to cases of the same clinical disease, the relation of carriers to such cases was more difficult to establish. Bronchopneumonias (46), the pneumonias of infants (195) and secondary pneumonias were usually found to be associated with Group IV pneumococci. In the pneumonias due to Type III, factors in the host were often found to play an important rôle (196, 197). In some focal purulent infections that are not complications of pneumonia, for example, primary meningitis or peritonitis, Types I and II were found, but Type III and Group IV pneumococci were predominant in most others (46, 191, 198). Under proper conditions, it is sometimes possible to trace the spread of Type III pneumococci in spite of this being a common carrier type (64).

Practically all of the new types have been found to be associated, in varying frequency, with pneumonia of all kinds and with focal infections. They have also been identified in normal individuals without infection. Types IV, V, VII and VIII have been found to be the most frequent of the new types in lobar pneumonia of adults (194, 197, 199-204). In bronchopneumonias, the type distribution is similar to that found in persons without pneumonia (199). In the pneumonias of infants and young children, Type XIV has been found to be most prominent and Types VI and XIX also rank high in frequency (45, 53, 66, 205-208). In the pneumonias complicating operations or trauma, the type distribution is intermediate between that found in normals and that found in

typical lobar pneumonia (209) In the pneumonias complicating pregnancy and the puerperium, the distribution of types is similar to that found in primary lobar pneumonia (210)

Multiple types of pneumococci may be found in the sputum and may sometimes be obtained from other sources in patients with pneumonia (53, 54 211) This is particularly true in infants and young children These multiple types or pneumococcus plus other organisms may represent either (1) true simultaneous infections, (2) consecutive infections or, (3) most commonly one of the types is etiological and the other is a normal carrier type (211) Certain types, when found in pneumonia, are usually etiological and when other types are found together with them the other types usually are not involved in the infection This varies, however, in different circumstances Thus in adults either Type I II or V when found in a patient with pneumonia, is usually etiological and others would be incidental In infants and children, Types I XIV V and VII have a similar status Other types may have an intermediate rôle, that is they may be the significant invader in some cases and merely incidental organisms in others Types VI and XIX pneumococci play this rôle in infants and young children In adults Type VI is one of the commonest carrier types and rarely gives rise to infection It is interesting that in experimental infections in guinea pigs, when they are simultaneously infected with Types I and XIX, only the latter gives rise to infection and remains as the carrier type while the Type I rapidly disappears In human beings, the relative pathogenicity of these types is the reverse namely the Type I is more pathogenic than the Type XIX and the former usually gives rise to the infection (104)

The most frequent types in pneumonia are Types I II and III and they are prevalent in most countries (50, 51 203, 204, 208, 212, 213), although their relative incidence varies in different localities (214) even in the same country⁴ The incidence of any one type as a cause of pneumonia may show wide fluctuations in different seasons in the same locality, independently of the general incidence (194 197 199 201) The distribution of types may also be influenced markedly by vaccination in any community where that procedure is carried out on a large scale (212 215-217)

In cases of pneumonia pneumococci have long been known to persist in the mouth for days or weeks after recovery (218) The causative organism, that is the same specific type is usually demonstrable for only a few days (2 to 3 weeks), but it may persist in some cases for several months (57 58, 184 185, 188, 189, 213) and occasionally for more than 2 years (62) The causative type in the patient is then usually replaced by a normal carrier type (184-189) In some of the patients who remain carriers for a long time, pneumonia of the same type may recur This was demonstrated in one case of Type II pneumonia by Cruickshank (62) and is probably the explanation for the high frequency with which the same type of pneumococcus is found in recurrent attacks of pneumonia that occur in the same patient within a few months (219)

Some differences have been noted in the persistence of the carrier state after

⁴ The distribution of types as gathered from the world literature is given on pp 23 to 30 of Hefron's book (8)

an attack of pneumonia in relation to the infecting types. For example, Stebbins and his associates (81) found that Type I pneumococci persisted for considerably longer periods than Type V. They suggested that this may account for the much smaller number of Type V as compared with the Type I carriers that they found in their study.

About one-fourth to one-half of normal persons having no contact with pneumonia have been found to carry pneumococci at any given time (46, 50, 51, 59, 60, 184, 189) and almost every person can be shown to carry pneumococci in the nasopharynx at one time or another if cultures are taken repeatedly (49, 56, 79, 87, 184). They are even frequent in infants after the first few months of life (220). In young infants, however, pneumococci are usually found only if they occur also in the mother. Seasonal fluctuations occur in the incidence of the pneumococcus carriers, and the peaks of incidence are highest for the types which are most intimately associated with pneumonia, namely, Types I and II (60, 189). The seasonal variations in the flora of infants and children is the same as in adults (221). It is rarely possible to trace the sources of carriers who have not had immediate contact with cases (59, 60).

Webster and Hughes (49) classified healthy individuals into four categories with respect to the finding of pneumococci in cultures from their nose and throat, namely, those who are pneumococcus-free, the transient, the periodic and the permanent carriers. How any one person fits into this classification may depend on the thoroughness with which the cultures are done and the number of times they are repeated (56, 62, 79, 87). At any rate, the same type or types may be found repeatedly in some persons, while in others they may appear intermittently and, in still others, different types appear and replace the earlier ones which are no longer found in subsequent cultures.

The most extensive study of the prevalence of pneumococci in different groups of individuals over several years was made by Straken, Hill and Lovell (194). They felt that if swabs are made frequently enough, most individuals will be found to harbor, even if only for a short period, most of the types prevalent in the area in which they live and work. These authors also noted that there is a tendency for each individual to establish a dominant flora containing one or more types of pneumococci, which tend to persist over considerable periods of time.

The presence of upper respiratory tract infections is not ordinarily a determining factor in the incidence of pneumococcus carriers (63, 79, 81, 222). Epidemics of such infections, however, tend to increase the spread of the disease-producing types, particularly in the families of cases. Gordon (223) noted instances of localized epidemics in which serologically identical strains were involved in all cases of a given group. The presence of persistent foci—in the nose, for example—also accounts for certain chronic carriers, both in human beings (45, 62, 224) and in animals (103, 104). Persons with simple respiratory tract infections who develop complications in the ears or accessory sinuses sometimes yield pneumococci in almost pure culture (225).

Among family contacts of cases of pneumonia there is almost always a very

high incidence of carriers of the same types of pneumococcus that are found in the cases (57-59 63 66 187-189, 222 226, 227) The highest incidence of contact carriers is found in the families of Types I and II cases (80) but other types may also be widespread among family contacts (48 80 226) Andrews (53b) found that Types I, V XIV and XXII showed the greatest tendency to spread by contact, Types III VIII, XIII and XIX showed little power to spread while other types, such as IV VI IX XI XVIII and XXIII were intermediate in this respect In the families of some cases every member has been found to harbor the same strain of pneumococcus

It is not usually possible to trace the spread of the carrier state within the household of a case The reason for this may be that studies of this sort are usually begun after the case is already established and at that time a high percentage of carriers is already found in the family (80) In fact it is uncommon to detect new carriers of the infecting type in subsequent surveys if adequate studies are made during the first survey of the family This fact has led Smilie to conclude that the case is not the primary source of the carrier but that the course of events in the family of a case is more often as follows A virulent strain of pneumococcus enters a family from without by way of one of its members, it spreads through the family often infecting all of its members, one of them becomes ill with pneumonia and we then become aware of the presence of the virulent pneumococcus in the family (80)

We have been able to trace such a course of events clearly when a single carrier of Type XXII pneumococcus was discovered in a large family which was being studied for the first time because of an outbreak of Type V pneumococcal pneumonia Although the latter type was found in almost every member of the household no other carrier of Type XXII pneumococci was discovered at that time Subsequently the Type XXII organisms spread to most of the other members of the family and gave rise to 3 cases of pneumonia The first carrier of this type had no evidence of recent infection, but nevertheless had a high titer of agglutinins for the homologous type (226) In our studies of family contacts of cases (226) we have almost invariably been able to demonstrate homologous type-specific antibodies in contact carriers of disease producing pneumococci at the time of the first observation, which was soon after the case became known This is indirect evidence that the organisms probably spread before the case arose The spread of Type I pneumococci in a community (81) and of Type XIV in a hospital ward (68) before the appearance of clinical cases of infection with these types has also been described recently

Carriers that probably arose from family-contact carriers have also been detected (59) In general the number of carriers produced depends on the intimacy of association with actual infection Family contacts have the highest incidence hospital contacts come next and then come the contacts of family carriers (59)

Buerger in 1905 noted that certain normal individuals could acquire pneumococci in their mouths while in hospital wards These pneumococci could be acquired either from pneumonia patients or from normal pneumococcus

carriers He also considered the handkerchiefs and eating utensils of pneumonia patients, and even of normal persons, as possible means of transfer of pneumococci from person to person He was able to recover pneumococci from a handkerchief one week after it had been used (218)

The percentage of carriers of homologous type pneumococci is usually much smaller among hospital contacts of cases, both patient and staff contacts, when compared with the high incidence of family contact carriers (63, 188) Nevertheless, a high percentage of carriers of disease producing pneumococci is often found among hospital contacts of pneumonia patients (62, 48) In one hospital, 18 per cent of the nurses on the pneumonia wards were found to harbor Type I and II pneumococci in their pharynx, whereas these types were not found in nurses of other wards to which pneumonia patients were not admitted (62) Other studies have also revealed a large number of carriers of these types under similar conditions, although the percentages are not so high (59, 189) The differences in these results may be attributable to the varying amounts of contact with cases and to the precautions taken against the spread of infection in the hospitals studied

PNEUMOCOCCAL INFECTIONS ACQUIRED IN THE HOSPITAL

Pneumonia is not usually considered to be one of the common nosocomial infections New types of pneumococci, however, not present at the time of admission to a hospital ward, have been shown to appear in the cultures of the nose and throat of patients during the course of their stay in the hospital (62, 66, 228) In addition, the change in the types of pneumococci recovered from patients with pneumonia during convalescence and the high incidence of disease-producing types of pneumococci among the nurses of pneumonia wards have already been mentioned It is to be expected, therefore, that some spread of pneumococcal infections from patients to the hospital personnel and to other patients, as well as from the personnel to patients, will arise The latter are probably the most frequent (228) Reports of instances of such infections in the earlier literature have already been mentioned, but the relation between those cases was not verified bacteriologically

Infections of this sort, which have been authenticated by finding the same type of pneumococcus in the contact case and its original source, have since been shown to occur from patient to physician (63, 229-231), from patient to nurse (78, 229, 231), from physician to patient (63, 232, 233) and from nurse or attendant to patient (229, 234) In some of the reports the circumstances surrounding the contacts are very clear and these contacts are known to be fairly long, repeated and intimate in some instances, while in others there was presumed to be a single and fairly brief contact Types I, II, III, VII and XXIII pneumococci were involved in the various groups of cases reported Nurses have acquired infection from cases, both in the hospital and on district duty (78) One case which was traced to a physician (232) was a pneumococcus Type I puerperal infection which clinically began in the hospital, but proved to have been infected from a district physician who had a respiratory infection and was found to harbor the Type I organisms

There is some evidence of the spread of human virulent pneumococci without producing clinical disease among the hospital personnel. The pneumococci spread either directly from patients or indirectly from other personnel who are in contact with patients (48, 62, 68). In some reports there is also indirect evidence offered that many infections in hospital patients arose from the personnel. In such cases, the new types which gave rise to the infection in the patients were found among the personnel, but the direct transfer of the given type was not traced in the individual cases (62, 228, 233).

There are several reports of cases of pneumonia due to specific types of pneumococci which arose on wards where other patients with pneumonia due to the corresponding types of pneumococci were being nursed (230, 231, 234-239). Types I, II, IV, V, VII, VIII and XIX pneumococci have each been implicated in one or more groups of such infections. Some of these pneumonias arose in patients while they were under treatment for other conditions in the same wards with pneumonia patients. Others were on the wards convalescing from pneumonia due to one type, at the time of the onset of a second infection with a different type derived from another patient. Usually the patient responsible for the second infection occupied an adjoining bed, but this was not always the case. A large proportion of the patients died as a result of the various infections acquired in the hospital wards.

The earliest well authenticated cases of bed-to-bed spread of type-specific pneumonias were described in the U. S. Army camps during World War I (238, 239). Cases of hemolytic streptococcal pneumonia complicating recovery from typical pneumococcal lobar pneumonia were also described in these camps (234, 238-242) and have since been observed in civilian hospitals (211, 237, 243-245). From the point of view of therapy it is also of interest that some of the recent secondary pneumococcal infections arose in patients while they were under treatment with sulfapyridine (236).

OUTBREAKS OF INFECTIONS WITH PNEUMOCOCCI OF SPECIFIC TYPES IN HOSPITALS AND OTHER INSTITUTIONS

In addition to the individual instances of pneumonia acquired in the hospital there are reports of a number of epidemics of pneumonia which occurred among the inmates and the personnel of hospitals for chronic or mental diseases, in children's homes, orphanages and other institutions (58, 64, 65, 68, 80, 246-249). We need consider only those in which epidemiologic studies included bacteriologic investigations and pneumococcus typing in the cases and preferably, also in the carriers in the search for sources of the infection.

Stillman (58) studied two epidemics of pneumococcus Type I pneumonia, one in a boys' asylum and the other in a state hospital. In the former the cases occurred in two dormitories and 10 per cent of the other infected boys in these dormitories were found to be carriers of Type I pneumococci. In the state hospital, 50 per cent of the cases and 10 per cent of the healthy contacts were found to harbor the Type I organisms. In both institutions, pneumococci of the same type were grown from the dust of the rooms.

Schroder and Cooper (65) reported a rather explosive outbreak of pneumonia,

bronchitis and colds in a children's home Type V pneumococci were isolated from almost all of the pneumonia cases in which bacteriological examinations were carried out This was the first time that a type of pneumococcus formerly classified in Group IV was shown to give rise to an epidemic Unfortunately, the minor respiratory infections were not studied bacteriologically In an outbreak of Type I pneumococcus infections in an orphanage, however, Ström (246) recovered this organism in cases of pneumonia, bronchitis and otitis media In this institution one-third of the children were shown to be Type I carriers at the height of the epidemic, and one-sixth of the inmates were still harboring this organism 10 weeks later There was also a high incidence of healthy Type I pneumococcus carriers in the community in which the orphanage was located, but none were found in three neighboring communities Joppich (247) also stressed the fact that pneumococci, even the Type I strains, can give rise to simple colds and catarrh The epidemic which he described occurred in a children's home The first case of pneumonia was complicated by Type I pneumococcal meningitis and empyema and the patient died There were 3 other cases of Type I lobar pneumonia within a few days At the same time, however, there were 21 other children ill with simple upper respiratory tract infections Type I pneumococci were identified in 15 of 30 persons in whom nasopharyngeal cultures were made The relation of the pneumococcus to the upper respiratory tract infections, however, is not clear It is possible that we are dealing here with an instance of the spread of pneumococci in the course of an outbreak of common colds, with the occurrence of pneumonia in a few of the susceptibles

A number of carefully studied institutional outbreaks of pneumonia have been reported in the last few years by Smillie and his co-workers (64, 68, 248, 249) In one of these epidemics (248), the spread of Type II pneumonia among patients and attendants was attributed to a number of carriers, who themselves remained apparently free of infection The epidemic abated during the summer months, but then recurred in different wards of the hospital during the fall The second outbreak was attributed to attendants who had been transferred in the meantime from the previously infected ward and proved to be persistent carriers The carrier state in the cases was found to be shorter than in the healthy carriers, some of whom harbored the organisms from 6 to 12 months The wife of one of the carrier attendants in this institution developed Type II pneumonia within a week of the time he visited at home, and the same organism was recovered from him shortly after this visit

An epidemic of Type I pneumonia in a state hospital (249) was also attributed to infections from carriers In this instance, the Type I pneumococcus carriers became widespread throughout the hospital during an epidemic of clinical influenza The cases of lobar pneumonia began to appear during the course of this epidemic and new cases continued to appear for several weeks After this outbreak had subsided, there occurred a fresh epidemic of Type I pneumonia in another branch of the hospital which was some distance away from the main hospital This fresh outbreak was traced to healthy convalescent carriers who

had been transferred from the main part of the hospital. Only one of the cases of pneumonia in this epidemic occurred in a carrier after the Type I pneumococcus was discovered.

Two small outbreaks were also reported in different schools for feeble-minded (64). In one of these institutions, Type III pneumococcus pneumonia occurred along with several cases of clinical influenza. Many of the attacks of influenza were found to be associated with pneumococci of the same type. This high prevalence of Type III pneumococci was limited to the one cottage in which an attendant had Type III pneumonia, and was not found in other parts of the institution which were similarly affected by the influenza. In the second school, there was an unusually high incidence of pneumonia and of pneumococcus carriers. The types among the carriers were grouped according to the types found in cases with which these healthy carriers came in contact, and the high incidence of these types accounted for the entire increase in the number of carriers. Types IV, V, VI and VII were the most prevalent.

In a recent outbreak in an orphan's home (68) Type XIV pneumococci were found to be widely prevalent in the children and nurses of one ward before the first infection with this organism became manifest in that ward. There had previously been cases due to this type on other wards. The Type XIV pneumococcus was recovered from cases of pneumonia, otitis media, conjunctivitis, bronchitis and simple respiratory infections, as well as from normal individuals. In the latter only small numbers of these organisms were found.

EPIDEMICS IN SCHOOLS, DORMITORIES AND PRISONS

Another epidemic of Type II pneumococcus pneumonia beginning in the course of an outbreak of upper respiratory tract infections was described by Dauer et al. (250). This occurred in a vocational school and was limited largely to one group of boys. In this group cases were found to occur in boys occupying cots next to persons who turned out to be carriers. The carrier rate varied from 10 to 44 per cent in various groups, the highest incidence being found in the group in which most of the cases occurred. Almost 3 months after the outbreak about one-fourth of the boys in the latter group were still harboring Type II pneumococci.

In this school, one case was reported in which the onset of pneumonia as judged by the initial chill occurred 6 days after the patient, along with a large proportion of the other pupils, received an immunizing injection of homologous pneumococcus antigen. Two of the epidemics described by Smilie (248, 249), one of Type I and the other of Type II pneumonia, were effectively terminated by the vaccination of the population of the institutions with antigens of the homologous types.

In the epidemic of Type I pneumococcus pneumonia studied by Wallbruch (251) the organisms apparently spread among the pupils of a village school during the course of an outbreak of 'grippe'. Some of the pupils became ill with pneumonia and most of the others had minor febrile illnesses. The school was then closed, whereupon the infection spread among the families of

the school children. Part of the family contacts then became ill and others became healthy carriers. Cases of pneumonia occurred in 13 of the 50 families of the village. There were 19 cases of pneumonia, all of which were shown to be due to Type I pneumococcus either by finding the organisms or by demonstrating the development of antibodies specific for this type, after crisis. About two-thirds of the family contacts of the cases were found to be carriers of Type I pneumococci and one-half of these carriers had mild upper respiratory tract infections. In the school population, which included 39 pupils and 1 teacher, there were 7 cases of lobar pneumonia and 18 more Type I carriers.

A somewhat similar spread of Type I pneumococci in a small community was reported by MacKenzie (56). Here the first case of lobar pneumonia appeared in a pupil in the primary room of the school. Three-fourths of the pupils in this room were found to be carriers of Type I pneumococci and they were shown to be the vehicle for the spread of these organisms through the village. There were only 5 cases of lobar pneumonia, but almost one-fourth of the population was discovered to be carriers. The principal determinant of the carrier state appeared to be the frequency, duration and intimacy of contact with carriers. Upper respiratory tract infections did not seem to play a significant rôle in the spread of the organisms in this outbreak.

Epidemics of Type I pneumonia were also described in each of two dormitories for transients located in widely separated parts of a large city (231). In one of these buildings, a second outbreak occurred after a lapse of several months during which no cases were reported. One of the patients in this outbreak had pneumonia twice with the same types. Careful studies were not made in these two institutions, but it is known that colds were highly prevalent in these dormitories. Type II pneumococcus pneumonias have also been reported with great frequency and in recurring episodes in a similar institution in another large city. In this institution there was also a high incidence of carriers of Type II pneumococci (252).

The finding of pneumococci in the floor filth of a prison in which pneumonia was highly prevalent (15) has already been mentioned. A high incidence of pneumonia and pneumococcal meningitis in jails has also been reported to occur in the tropics (253). Bonne (254) reported a large number of cases of pneumonia in a temporary prison in the Netherlands Indies. The disease in his cases was exceedingly severe and was associated with a high fatality rate as well as a high incidence of focal pneumococcal complications, such as pericarditis, meningitis and peritonitis. New arrivals were found to be particularly susceptible. More than one-third of the cases were due to Types I and II pneumococci, but no Type III cases were encountered. Prophylactic vaccination with a mixed vaccine containing Types I and II organisms markedly reduced the incidence of pneumonia and carriers of these two types among the inoculated prisoners. When a new batch of carriers was transferred from another prison, the carrier rate in the inoculated group increased much more than among the uninoculated.

An outbreak of pneumonia reported from a German prison camp during World War I is also of interest, even though it was not due to the pneumo-

coccus (255) In this camp, every case that was studied bacteriologically, without exception, proved to be due to the Friedländer bacillus In many of the cases, these organisms were recovered in almost pure culture for many days In a few cases pneumococci and streptococci were also found, but the Friedländer bacillus was predominant even in these cases There were 441 cases with 144 deaths in less than 5 months Purulent complications and recurrences were encountered in some of the patients

SPREAD OF PNEUMONIA IN CERTAIN INDUSTRIES

Pneumonia is known to be unusually frequent among workers in certain mining (34, 35, 212, 215, 256-260) and milling (78, 261-264) industries and in relation to some other occupations⁵ (33, 265-268) In the case of certain mills this may be associated with a high incidence of carriers (78, 262) which, in turn, may occasion an outbreak of pneumococcal infections in the community (78) In others, the conditions of the work may predispose to frequent or chronic respiratory tract infections, because of inhalation of irritating dusts or because of unusual climatic exposures (260, 263, 266, 268) Coughing and sneezing may then result in the spread of respiratory pathogens among the workers by droplet infection (263)

In certain mining regions and in some other occupations, the determining factor in the spread of the disease may be the living conditions of the employees, rather than any circumstances surrounding the work itself This has been found to be true in a certain group of steel workers who lived in small shanties (267), among the construction group at Panama (33, 34), among the plantation workers in the tropics (265-269) and in the mining communities in South Africa (34, 35, 212, 256-259) The crowding and intimate contact in the sleeping and living quarters offer the greatest opportunity for the spread of respiratory pathogens Epidemics have been noted in the barracks (261, 269) and among the families of workers (78, 261) Investigations in South Africa, for example, revealed no evidence of case-to-case infections in native miners working in the same gang underground, but multiple case infections in the same room in the living quarters were more than could be expected from the law of probability (259) In all these industries, the newly arrived workers usually prove to be the most susceptible (34, 260) Bacteriologic studies have usually brought out the contagious factor in persons living in the same shanties or barracks Only those workers who have failed to carry out such studies have minimized this factor (35, 268) Many of the pneumonias occurring in industries are considered to be preventable (6)

THE SPREAD OF PNEUMONIA IN MILITARY AND OTHER CAMPS

Pneumonia was the leading cause of death in the army camps in this country during World War I (238, 270) The most severe outbreaks of pneumonia that took place in these camps and accounted for the greatest proportion of this mortality occurred in relation to epidemics of measles (238-242, 271-276) and

⁵ See also Hefron (S), pp 318 to 332

of influenza (238, 239, 275, 277-280), and were almost always associated with hemolytic streptococci. These pneumonias were usually atypical bronchopneumonias that first began to appear in the camps while the other epidemics were prevalent and continued to occur after the latter had abated. In addition, in some of the camps numerous cases were reported in which hemolytic streptococci were found to give rise to mixed infections or to secondary infections in cases of typical pneumococcus lobar pneumonia (238, 240, 242, 276, 279-282).

The spread of hemolytic streptococci in the throats of patients admitted to pneumonia wards was shown by the incidence of positive cultures which increased progressively during the patient's stay in the wards. In some instances, hemolytic streptococci were cultured from the dust of the wards (276). It was not usually possible, however, to trace the exact sources of contagion, because the hemolytic streptococci could not be classified at that time. In some of the base hospitals, the character of the pneumonias changed abruptly from typical pneumococcal lobar pneumonia to the streptococcal varieties without other intervening epidemics (272, 282). In addition, not all of the epidemics of influenza were complicated by hemolytic streptococcal pneumonias (278).

Although the epidemics of hemolytic streptococcal infections were highly important, the great majority of the cases of pneumonia that occurred both before and after these epidemics, and many that occurred while they were still in progress, were typical pneumococcus lobar pneumonias (238, 240, 242, 279-287). As a matter of fact, many cases of lobar pneumonia occurred in the regular Army during the Mexican War (273, 283, 284), and from a study of some of these cases it was predicted that outbreaks would occur after the mobilization (283). Some outbreaks of pneumonia and other pneumococcal infections were also described among Colombian soldiers in 1914 and 1916 (269). Many outbreaks of such cases were recorded in the various army camps in this country. A number of the reports contained careful epidemiological and bacteriological studies. The results of some of these studies may be summarized briefly.

Types I and II pneumococci were by far the most frequent types isolated from sputum, blood and purulent complications, and from the lungs and other sources at autopsy. Individual types predominated in certain camps or isolated outbreaks. Epidemics of Type I pneumococcus pneumonia were reported from Camp Jackson (285) and Camp Upton (287), and an unusually high prevalence of Type II cases occurred in Camp Grant (279, 280).

In many of the camps there was evidence of direct contagion. The cases tended to be grouped in tents, in companies and even in regiments. Direct contagion was demonstrated only when pneumococcus typing was employed. Cultures of healthy contacts also revealed a higher percentage than would be expected of carriers of the disease producing Types I and II pneumococci (284, 286). Unusual numbers of such carriers were sometimes found in individual units (239). The spread of pneumococcus pneumonia from bed to bed could be traced in some hospitals (234, 238, 239), as already mentioned. Type II pneumococci were especially prominent as secondary invaders in such cases.

New draftees were especially prone to develop pneumonia and those among southern negroes tended to be the most susceptible. In some camps the latter accounted for almost all of the cases of pneumonia occurring during certain months (275).

Two of the epidemics of Type I pneumonia are of especial interest. In one, the outbreak was limited to a group of laborers who had recently arrived directly from Puerto Rico (285). There had just been an epidemic of upper respiratory infections at the camp and this spread rapidly among the Puerto Ricans attacking about two-thirds of them. Atypical pneumonias appeared during this epidemic and later there appeared cases of typical lobar pneumonia with Type I pneumococcus predominating. The second Type I outbreak is of interest because it occurred in troops that had just returned to camp from overseas for demobilization (287). Outbreaks of pneumonia are also described during the demobilization after the War of 1912 and these are supposed to have been spread to different communities by the returning soldiers (288).

Epidemics of pneumonia have also been described in nonmilitary camps. The outbreak of Friedländer's pneumonia that occurred in the German prison camp has already been noted (255). Harris and Ingraham (77) studied an epidemic of Type II pneumonias in a camp of the Civilian Conservation Corps. This began in the fall with a series of upper respiratory tract infections, after the men had been confined to their barracks for several days because of rainy weather. Each of the five barracks in this camp had 1 or 2 cases and from 4 to 8 carriers. Among the officers there were only 2 carriers and they had had the most contact with the men. No carriers were detected among the foresters who lived in separate quarters. In 25 per cent of the carriers a direct contact could be traced with a case, either shortly before or during the infection. Type II pneumococci persisted in some of the carriers for at least 10 weeks. One of the cases developed Type II pneumonia 6 days after a culture was made which revealed only Type XXII pneumococci. Immunological studies revealed some instances in which the carrier state was correlated with the presence of a high titer of the homologous type-specific antibodies.

MULTIPLE CASES OF PNEUMOCOCCAL INFECTIONS WITHIN A FAMILY

It has already been noted that in the families of cases of pneumococcal pneumonia there is a very high incidence of carriers of the same types of pneumococci as are found in the cases. It is not surprising, therefore, that multiple cases of pneumonia occur in the same family. Many instances of family outbreaks of pneumococcal infections due to the same type of pneumococcus have been reported (48, 62, 78, 226, 229-231, 234, 235, 237, 289-295). The types recorded in these groups of cases include Types I, II, IV, V, VII, VIII, X, XII, XIV, XIX, XXII and XXIII. While lobar pneumonia was the predominant pneumococcal infection in the different members of the various families concerned, there were instances in which the pneumococcus gave rise to atypical (broncho-) pneumonias, meningitis, otitis, conjunctivitis or arthritis in different members of the same family (78, 226, 292). Instances are also on record of lobar pneu-

monia due to the same type in twins (237, 289-291) and of pneumococcal infections transmitted from mothers to newborn infants (296)

Upper respiratory tract infections are usually prevalent in the families where multiple cases of pneumonia or definite focal pneumococcal infections occur. Since most of these persons with simple infection also carry the pneumococci of the homologous type, it is not usually possible to ascertain whether the pneumococcus is etiologically related to such infections. The development of type-specific antibodies in such cases would suggest that they may be related (226)

Most of the cases occurring in the same family have the onset of their infections within a few days of each other (297), suggesting that they probably arose from a single source outside of the household. It is also possible, as already noted, that one healthy member of the family becomes a carrier after contact with an outside case or carrier, and then infects the different members of his household more or less simultaneously. The susceptibles then get manifest infection and the others become carriers. If it happens, however, that the first person to have contact with a new and virulent type is also susceptible, then he will get a manifest infection. This course is the less frequent, because most persons do not get ill on each contact with such pneumococci.

The secondary attack rate for Type I infections was found to be highest in infants and in children under 4 years, and to decrease in the succeeding childhood and adolescent age groups (78). For all pneumonias in a large part of New York State, on the other hand, relatively high secondary attacks were found only in the extreme age groups (297). Of the secondary attacks in the latter series, 60 per cent occurred in the first week, and younger members of the household acquired the secondary infections more promptly than older ones. Definite secondary cases due to the same type and arising from contact with convalescent carriers in the household have also been reported (62, 231). There are also instances of pneumonia acquired in the household of cases by persons outside of the family who come in to help with the household duties (235, 295).

The effect of crowding in the homes on the incidence of pneumococcal pneumonia in a community has been shown (298), but this has not been correlated definitely with secondary attacks in families. In fact, only families with two or three members have shown a secondary attack rate much above the average. In such families, of course, the most intimate contact is to be expected (299).

PNEUMONIA ACQUIRED IN THE LABORATORY

This is probably a very rare occurrence. Robertson (300) reported a case of a laboratory assistant who acquired pneumonia on two occasions 5 months apart. The first attack occurred from 30 to 36 hours after he washed a jar that had been used for spraying experiments with Type I pneumococci. The second attack began about 40 hours after he was sprayed with Type II pneumococci that spurted from a syringe. These may both have been instances of direct droplet infection, although it is possible that the first was acquired through handling the organisms. The latter method was assumed to be the mode of infection in 2 other reported cases (231). One was a technician with hay fever who developed a Type I otitis media after handling her handkerchief at the same time

that she was working with pneumococci. The other had an upper respiratory infection and was putting cough lozenges into her mouth while handling a mouse infected with Type VII pneumococcus. Three days later she had the onset of lobar pneumonia due to this organism. The writer has also observed four instances of pneumococcal pneumonia acquired in the laboratory through the handling of sputum from patients. Two of these were Type I infections, one was Type II and the fourth was Type XVIII.

THE RÔLE OF IMMUNITY IN THE EPIDEMIOLOGY OF PNEUMOCOCCAL INFECTIONS

Antibodies to pneumococci can be demonstrated by various methods in a large proportion of human beings (220, 301-306). Thus, fresh defibrinated blood of most humans has some bactericidal power against many types of pneumococci. This property may, in the same individual, vary both qualitatively and quantitatively for different types of pneumococci. For each type, however, pneumococidal power is present in the blood of infants during the first few days after birth with about the same frequency as in adults. Each infant resembles its mother in this respect. This pneumococidal property is apparently lost by the end of the first month, and can not be demonstrated again until after the first year. It is less frequent in children than in adults and declines again in persons over 60 years of age (304, 305).

Blake (306) found nontype-specific agglutinins in human serum. The curve of incidence of such agglutinins in the various age groups seemed to mirror the morbidity rates for pneumonia in the same community—that is, the morbidity was highest in the age groups in which the least agglutinins were found, and vice versa. In this respect it was similar to the curve of incidence of the bactericidal power of normal fresh defibrinated bloods against type-specific pneumococci (304).

Felton (307) demonstrated mouse protection antibodies against one or more lethal doses of Types I and II pneumococci in the serum of almost one-third of some 1100 human subjects. He found protection against 100 or more lethal doses (in 0.1 cc. of serum) in 9.6 and 11.7 per cent of subjects against Types I and II pneumococci respectively. Others had also found such antibodies, with varying frequency, in small groups of normal human serums (61, 304, 305, 308). Agglutinins for type-specific pneumococci, however, are rarely detected in normal serums (77, 304, 305).

Immediate positive skin reactions to type-specific polysaccharides (309) are also infrequent among normals (77, 304, 310). On the other hand, the delayed tuberculin-like reaction to the acetic acid precipitable pneumococcus nucleoprotein can be elicited often in normals. The frequency of such positive reactions seems to increase in advancing age groups (304) and resembles the frequency of similar reactions elicited with streptococcus nucleoproteins (311).

Differences in the frequency with which antibody reactions are elicited with the various tests seem to depend on the sensitivity of the tests employed. These differences appear to be even more striking among normal subjects than among immunized individuals (310) or among patients recovering from pneumonia (312). The ability to produce antibodies as a result of the stimulus of

infection or of immunization with pneumococcus antigens seems to vary considerably. Among infants and young children particularly, antibodies are demonstrable with much less frequency and in considerably lower titers after infection (61, 313, 314) or after immunization with specific carbohydrates (315, 316). Felton (307) found that 5.5 per cent of normal individuals had no demonstrable protective antibodies whatever against Type I, and 1.1 per cent had none against Type II pneumococci after immunization with his antigenic polysaccharides. After immunization of the same subjects, the serums of 12.8 per cent failed to protect mice against 100 or more lethal doses of Type I and 4.9 per cent failed to protect against similar doses of Type II pneumococci. None of Felton's subjects in this particular study were under 2 years of age and very few were under 10. He felt (317) that the individual variations in response to his pneumococcus polysaccharide antigen are important factors in the relative resistance to pneumococcal infection.

It is usually assumed that the antibodies demonstrable in normal subjects are present as a result of previous exposure to pneumococci, that is, as a result of manifest or latent pneumococcal infection. There are, of course, other possible explanations (304) that need not be considered here. That antibodies may develop as a result of the carrier state alone, without intervening infection, has been demonstrated in the course of investigations of contacts of pneumonia cases in families (226, 235), in hospital personnel (79) and in a camp of the Civilian Conservation Corps (77). Contact carriers are usually detected only some time after the cases are known to occur. In such carriers, antibodies specific for the type of pneumococcus found in any given case and its contacts are usually detectable by the time the carrier state is detected. In occasional instances, however, it has been possible to detect the development of antibodies after the pneumococcus was first cultured (79, 226). Antibodies to pneumococci may also result from an immune response to antigenically related organisms or substances.

Since, as already noted, more than one-fourth of all normal persons carry pneumococci at any given time and almost all persons carry them at one time or another in the course of the year, such carriers probably represent those who respond well to pneumococcus antigens and are therefore highly resistant to infection. This may explain why only 1 in 500 persons contracts pneumonia (317).

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respiratory tract infections such as the common cold or clinical influenza which are presumably of virus origin precede pneumonia in a large proportion of cases. It has already been noted that such infections increase the spread of virulent disease-producing pneumococci. It is not unlikely that these virus infections also bring about some alteration in local tissue immunity of the host or act in some other way to permit invasion by pneumococci even in a partially immune individual.

PREVENTIVE VACCINATION AGAINST PNEUMONIA

The most extensive and prolonged experiments in preventive vaccination have been carried out in the South African mining communities (215-256-259). Similar experiments were carried out in some of the United States Army camps during the first World War (216-217). Polyvalent whole pneumococcus vaccines killed in various ways were used in these investigations. Similar vaccines have also been used on a smaller scale in a prison population (254) and in an industrial community (264) where there was an unusually high prevalence of pneumonia. The results obtained from all these trials were in a general way quite similar. The incidence of the pneumonias associated with the types of pneumococci that have been incorporated in the vaccine was lower in the inoculated individuals. New pneumococcus types however kept appearing and other organisms also became more frequent in the inoculated communities (256-257). In one of the mining communities vaccination was discontinued at a time when the lowest pneumonia death rates had been attained. Following this, there was a steady rise in pneumonia incidence, and epidemics occurred in which some of the pneumococcus types formerly included in the vaccine were again predominant among the cases (258).

Mixed vaccines, containing pneumococci, hemolytic streptococci and other respiratory organisms have also been used for the prevention of pneumonia and other respiratory infections. The results however are difficult to interpret, although some workers felt that they were encouraging enough to continue trials with them (323).

Felton in cooperation with the United States Army and with officials of camps of the Civilian Conservation Corps immunized 60 000 volunteers with his polysaccharide antigens and had 72 000 controls. There was a reduction of 50 per cent in the incidence of pneumonia among those injected and the mortality in the immunized group who contracted the disease was lower than in the controls (324).

¹ A more recent study by Segel and Muehlenfuss (330) has brought out the many difficulties involved in evaluating the results of immunization against pneumonia. These authors felt that even Type I pneumococcus pneumonia was not prevented by immunization with pneumococcus polysaccharides. Kaufman (331) reported results of active immunization with a combination of Types I and II pneumococcal capsular polysaccharides (1 mg. of each given subcutaneous) against old age pneumonia in 1750 subjects conducted over a 2-year period. He demonstrated a reduction in the incidence and mortality rates among the inoculated but no appreciable effect on the case fatality rates. The prophylactic value seemed more pronounced in the first three quarters than in the last quarter of the year after immunization.

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as a single injection intraperitoneally, followed by two local washings. Neither drugs nor serum when given by one of the routes alone were effective.

Reports on the effects of sulfonamide drugs on the carrier state are not yet available. The rapid disappearance of pneumococci from the sputum of patients with pneumonia while under treatment suggests that use of the drugs in therapeutic doses might prove useful. Local treatment may prove helpful as an adjunct to the general use of the drugs but it is not likely to be effective alone. Chronic carriers who have foci of infection in the respiratory tract are not likely to be influenced by the treatment unless these infections are eliminated.

SUMMARY AND CONCLUSIONS

The collected reports concerning the spread of pneumonia and of pneumococcal infections may be summarized briefly.

Evidence for the contagious character of pneumonia has been available for a long time and it has been thoroughly authenticated with the aid of modern bacteriologic methods. Both cases and carriers are responsible for the spread of pneumonia and of other pneumococcal infections, but the carriers are more numerous and probably account for the bulk of infections in the community. The occurrence of pneumococcal infection in any given person is dependent on that individual's susceptibility to the particular strain of pneumococcus with which he comes in contact. The factors underlying this susceptibility are not clearly understood. The degree of spread of the infecting agent, however, is probably directly proportional to the amount and intimacy of the contacts with cases or carriers. The spread of disease-producing pneumococci is greatest within the family, in barracks and in open dormitories where persons have the most intimate and most prolonged contact. There is evidence that disease-producing pneumococci may survive in air or dust. Except for the rare instances of laboratory infection, however, there is very little direct and positive proof of pneumococcal disease in man acquired through droplet or air-borne infection.

MEASURES RECOMMENDED FOR CONTROL OF THE SPREAD OF PNEUMONIA AND OF PNEUMOCOCCAL INFECTIONS

Most of the important general preventive measures designed to minimize the spread of pneumonia and to control the mortality from this disease were drawn up in 1917 by the Rockefeller Institute workers (36) and are equally applicable today. Their recommendations were based on extensive studies made possible by the classification of pneumococci, and may be summarized briefly.

Education of the medical profession and of the public concerning the danger of the spread of pneumonia by contact with cases, direct or indirect, is essential.

General compulsory reporting of cases is recommended in order to ascertain the incidence and focal distribution of cases (327).

Since certain types are particularly important, the widespread application of *pneumococcus typing* by hospital and health department laboratories is highly desirable. This would supply additional important epidemiologic data.

Vaccination with type-specific vaccines and with specific pneumococcus polysaccharides has also been employed during the course of epidemics of pneumococcal pneumonia in various institutions (248-250). Under these conditions the vaccines appear to be highly effective. New cases of pneumonia due to the same type of pneumococcus rarely appear after more than 6 days have elapsed following inoculation of the exposed population with the antigenic material of the homologous type.

The immunity resulting from vaccination with whole pneumococcus antigens is predominantly type-specific, and the transferable antibodies are almost entirely so. There is some evidence, however, from the animal studies previously mentioned, that some degree of resistance to actual infection with heterologous types of pneumococci may develop, although this may not be measurable by mouse protection or other immunological tests. Felton (316) has obtained a Type I antigen which is specific in mice but which produces antibodies in almost equal titers against Type II in human beings and, conversely, an antigen which he has prepared from Type II pneumococci produces antibodies in equal amounts against both Type I and Type II pneumococci. This is contrary to the findings of many other workers, although similar results have been recorded by occasional investigators (325).

How long resistance to infection persists after vaccination is not known, but it certainly varies widely in different individuals. Protective antibodies have been demonstrated in a majority of the subjects tested as long as 1 year after inoculation with Felton's antigens (316).

TREATMENT OF PNEUMOCOCCUS CARRIERS

Since carriers have been shown to play an important rôle in the spread of pneumonia, attempts have been made to treat such carriers with a view to eliminating the pneumococci from the upper respiratory tract. Since pneumococci are so widely prevalent, however, it is obviously necessary to limit the treatment at best only to convalescent carriers and to those who harbor the common disease-producing strains, such as Types I and II. This has been recommended during periods of unusual prevalence of pneumonia or of simple respiratory infections, particularly where large numbers of susceptibles are brought together (177, 286, 326).

Sailer et al (286) isolated a group of both healthy and convalescent carriers at Camp Wheeler and tried various gargles, sprays and instillations. He found dichloramine-T or iodine in oil, used as a spray or for instillation, to be the treatments of choice. The use of quinine sulfate apparently protected against influenza, but did not affect the carrier state. Kolmer and Steinfeld (326), on the basis of *in vitro* studies, recommended gargles of 1:10,000 ethyl hydrocupreine in a 1:10 dilution of liquor thymolis, and also suggested Dobell's solution for douching or spraying the nose.

Neufeld (177) studied the problem in guinea pigs, which are known to become chronic pneumococcus carriers either spontaneously or after intranasal infection (103, 104). He found the most effective treatment to be specific serum given

possibility of late infections from convalescent carriers discharge cultures are recommended (231) and proper instructions should be given to cases with positive cultures to avoid the spread of the organisms

Prophylactic Inoculations Since it has been shown that the spread of any given epidemic when caused by a pneumococcus of a specific type can be halted by vaccinating the entire exposed population with the homologous type-specific vaccine this is strongly recommended under such conditions. Whether widespread vaccination before outbreaks appear will prevent the occurrence of epidemics is not yet certain. The experiments already mentioned particularly those carried out in South Africa indicate a definite field of usefulness for vaccination if properly applied in communities where a high prevalence of pneumonia is expected

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Each case should be regarded as a possible focus of spread, and measures found useful in other communicable diseases should be applied. The patient should be isolated and prevented from contact with other persons as far as possible (cf 328)

Since pneumococci spread mostly by way of the secretions of the mouth and respiratory tract, care should be taken in collecting sputum and burning or disinfecting containers. All utensils, handkerchiefs, bed clothing, etc. which are likely to become contaminated through contact with the mouth should be sterilized before they are used again.

Frequent cleansing of the sickroom, carried out in such a way as to minimize the amount and spread of dust, is important. The sickroom should be cleaned thoroughly after it is vacated by the pneumonia patient.

While the control of convalescent and healthy contact carriers of disease-producing types of pneumococci through isolation would be desirable, it is not practicable. Carriers, however, may be instructed to avoid promiscuous spitting. The use of disinfectant mouth washes may also be useful in healthy carriers (cf 323).

Under conditions which are most suitable for the spread of pneumococci, namely, in dormitories, barracks, hospitals, asylums, labor compounds, prisons, etc., these preventive measures may be especially important and should be applied as soon as the first cases are recognized. Search for carriers among the contacts of the cases should be undertaken immediately. Isolation of the carriers, or at least precautions instituted to prevent further spread by them, should be carried out.

Most of these precautions have been reiterated by others who have been impressed with the contagiousness of pneumonia (48, 62, 231, 235, 236, 242, 251, 254, 258, 283, 294, 328). A few additional points have been made on the basis of individual experience.

Cole and MacCallum (242) recommended the segregation and protection of cases of primary lobar pneumonia (due to pneumococcus) from cases of hemolytic streptococcal infections. This is highly important during epidemics of the latter, especially when associated with measles and influenza.

Nichols (283) stressed the importance of having army camps equipped to handle epidemics of pneumonia, and this was appreciated by all the medical officers during the last World War.

The application of isolation precautions to carriers of Types I and II pneumococci, especially during outbreaks, has frequently been urged (62, 329).

The predisposing factors leading to the spread of pneumonia in industries must be studied carefully in each instance, and attempts made to eliminate these factors as far as possible.

Woods (6) believes that the mortality from pneumonia would be reduced by more and better hospitalization, but the reasoning upon which this belief is based is open to question.

Strict isolation and individual technique have been recommended for cases of lobar pneumonia to avoid cross infections (62, 231, 236, 239). Because of the

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PHYSIOLOGY OF MUSCULAR EXERCISE AND FATIGUE IN DISEASE

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PHYSIOLOGY OF MUSCULAR EXERCISE AND FATIGUE IN DISEASE

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INTRODUCTION

Loss or impairment of working capacity is by definition characteristic of disease, restoration of working capacity is therefore the general purpose of therapy. Loss or impairment of working capacity is by definition an important feature of fatigue. Fatigue is one of the most common complaints from patients. It is important to distinguish between subjective complaints and the objective demonstration of fatigue. It is plain that clear distinctions between real demonstrable fatigue and complaints of fatigue must be established by precise objective methods, and since we have defined fatigue as "reduction of working capacity" methods must be developed which will measure working capacity in terms of its components. The same principle should be applied to the analysis and discussion of the experimental material, accordingly, the use of the very general term "fatigue" has been avoided and the discussion restricted to definite functions, such as oxygen intake, efficiency, etc., on which working capacity and fatigue depend.

There is no fundamental physiological process which is not involved in muscular work. Consequently, the deterioration of any fundamental process will disturb the coordinated and integrative function of the whole organism during muscular work and thus lead to a decrease of the general working capacity. Fatigue may be due to the impairment of several quite different functions concerned with various types of work. It is to be expected, therefore, that working capacity will be decreased by diseases to a different degree in different types of work. A thorough analytical breakdown of working capacity into its elements is really essential in order to clarify these problems. An important step of practical significance in the analysis of working capacity is the investigation of patients with chronic diseases in different types of work. There are, in this country, several million people suffering from chronic diseases and limited working capacity. On the basis of an analysis of the effect of diseases on performance in various types of work it might be possible to advise patients with chronic diseases towards occupations where their working capacity would be least reduced or which would be least injurious. At the same time, control of the taxation of their working capacity would be good treatment for their condition.

It is clear that investigation of muscular work and fatigue is of first importance in patients with chronic diseases. It is in such patients that the diminution of working capacity has practical or clinical significance. In acute infectious diseases the period of convalescence is important too. It is known that patients after complete disappearance of clinical signs and symptoms of the infection have often not yet reached their full working capacity. Without systematic investigation of patients during and after muscular work, our judgment regarding their working capacity is quite arbitrary. In chronic diseases discrep-

ancies between the clinical findings and the actual working capacity are rather frequent. This is due to the fact that the state of the patient does not depend only on the primary lesion, but also on the numerous compensatory mechanisms provoked by the disease. All authors who have worked in this field agree that investigation during work permits a much better understanding of the patient's actual condition than an examination during rest. The patient may still be fully compensated while at rest but not so for the increased demands during and immediately after muscular work. Thus the investigation of patients by means of exercise tests is especially important for those on the verge of cardiac compensation i.e. apparently recovered from decompensation. This stage is from the point of therapeutics, perhaps the most important. After a patient once has experienced a cardiac decompensation it is very difficult if not impossible, to restore his working capacity to the level of the prebreakdown state (Altschule). Study of the most important physiological functions during muscular work might reveal earlier symptoms of decompensation or the inclination to decompensation than would be possible to uncover by investigation during rest. All signs and symptoms (for instance in heart disease—dyspnea orthopnea edema) result from the impairment of a multiplicity of closely inter-related bodily functions so that there is no complete and dependable correlation to anyone of them (Altschule). The maintenance of some elementary or fundamental functions is obtained at the price of impairment of other functions. For instance, the increase of the venous pressure and diastolic heart volume in hypodynamic hearts will improve the economy of the working heart and help maintain a sufficient stroke volume. On the other hand many vicious circles occur at the same time, for instance edema resulting from anoxemia impairs the oxygen diffusion to the tissues (Harrison and Pilcher (109)). Thus, the state of the patient during clinical compensation as well as during decompensation must be viewed as a complicated and intrinsic integral of various functions involving mutual compensations as well as decompensations. It seems that the state of the patient depends more on the interrelation of several functions than on any single function alone. Thus decompensation may break through at any point in this complicated system of regulations, in the periphery as well as in the heart itself. Investigations during muscular work will help to recognize the weakest point at which a decompensation is most likely to occur and thus contribute essential information for therapeutic procedures.

In the last 40 years an increasing number of authors have investigated patients with different diseases during and after muscular work. This field has never been systematically and critically reviewed, although the number of investigations is already quite considerable. We, therefore, thought it worth while to undertake such a review. As most investigations concern gaseous exchange, circulatory and respiratory functions, the review has been restricted accordingly. Chemical and physico-chemical and nervous processes will be reviewed later. In regard to reviews on normal physiology of exercise and fatigue we refer readers to Atzler (8-10) Bambridge, Dill (63-64) Schneider Simonson (243-245) Steinhaus and McCurdy and Larson.

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and that disease of the aortic valve in itself does not give rise to symptoms. The German ski champion of 1924 presented signs of aortic regurgitation (Parvus). Parade describes three young athletes with aortic regurgitation who performed excellently as football player, cyclist and ski runner.

Jokl (139) reported a man with aortic regurgitation of syphilitic origin who was able to carry out most strenuous industrial work, and Suzman observed a man with aortic insufficiency of rheumatic origin who excelled in long distance swimming. Jokl (141) and Suzman described aortic regurgitation and mitral stenosis in a marathon runner. His time for the race represented a performance of international merit. His condition after the race was surprisingly good and his recovery time was short as compared with that of other competitors. Jokl and Suzman hold that mitral stenosis alone reduces working capacity much more than when combined with aortic insufficiency. Proger and Korth arrive at similar conclusions. Outstanding athletic performances have been observed by Herxheimer (125), and by Liljestrand and Zander in patients with total heart block. Heilman reported a soldier of 23 years of age with a large aneurysm of the aorta, who had successfully participated in long distance walks and races without any clinical symptoms.

A very important contribution to this question is that of Jokl and Melzer (140), based on a material of 64 autopsies in cases of acute fatal collapse during work and athletics. Among these cases were seven with outstanding athletic performances in football, long distance running, tennis tournaments, etc. Necropsy revealed serious pathological alterations of the heart with only one exception. They never had any complaints or symptoms. We are able to confirm fully these findings with several similar (unpublished) cases illustrating a marked discrepancy between advanced anatomical disease and outstanding performance in heavy occupational work or athletics.

It is interesting that severe lesions of the heart do not necessarily impair maximum performance for muscular work. It is clear that the impairment for types of moderate exercise will be still less pronounced so that the number of patients with pathological lesions of the heart, but without any clinical signs and symptoms, may be quite considerable. Such cases will seldom be diagnosed during life. This leads to the conclusion that lesions of the heart may be fully compensated not only for resting condition, but also for maximum performance, and that it is not the primary lesion, but the breakdown of the compensatory mechanisms which leads to the clinical signs and symptoms of circulatory insufficiency.

C Methods to Measure Maximum Working Capacity

1 Rate of Maximum Oxygen Intake There is a linear relationship between maximum oxygen intake and maximum working capacity in normal subjects as well as in patients with heart or pulmonary diseases (Herbst(119-121), Knipping(157)). Therefore the maximum oxygen intake may be expressed by the amount of meter kilos and vice versa, but this can be done only when the same type of standard work is used.

The absolute value of the maximum oxygen intake depends on the body

I MAXIMUM WORKING CAPACITY IN DISEASE

A Definition

We have defined disease as "diminution of working capacity." Hence the measurement of the maximum working capacity should be an ideal method by which to determine the extent of the damage produced in the organism as a whole by pathological processes. Investigations into the deviation of single physiological functions under pathological conditions are important in the analysis of the fundamental components of working capacity, but it is impossible from such data to arrive at comprehensive conclusions concerning the "complex" of working capacity, because of the intrinsic compensation and decompensation mechanisms involved in disease. The principal factors determining maximum working capacity are "intensity" and "endurance." Maximum intensity of work (m-kilos per second) is greater, the shorter the duration of work. If maximum performance is accomplished in the anaerobic period (durations of work up to 30 to 40 seconds), it does not depend on the circulatory or respiratory function, because the duration of work is shorter than the time necessary for the blood to accomplish one complete circuit. Very few experiments on patients have been made to determine the maximum capacity of anaerobic work.

In types of work where a considerable energy expenditure is maintained for a longer period of time (at least 20 to 30 minutes or more), the limit of performance is determined by "endurance" and is directly related to carbohydrate exhaustion.

In pathological physiology those types of work are most important, where the maximum capacity for work (determined by the maximum amount of m-kilos per minute) is limited by the maximum intake of oxygen. In normal conditions this depends on the maximum minute volume of the heart. Therefore, in such exercise, maximum working capacity can be defined and measured by maximum oxygen intake. Maximum oxygen consumption can be attained only in types of work where a sufficiently large number of muscles is involved.

B Outstanding Athletic Performances in Patients

The maximum working capacity need not be diminished at all in compensated valvular or other lesions of the heart, in mild diabetes, etc. On the contrary it is known that "patients" with well compensated valvular heart disease may perform athletic feats far exceeding those of average healthy subjects. Herxheimer (125) saw many patients with mitral or aortic insufficiency who repeatedly performed in competitive athletics without ill effect. The question of damage as a result of athletic indulgence and severe physical effort will be reviewed elsewhere. On the other hand, patients with mitral stenosis, even if they are able to carry out considerable athletic performances, usually experience diminution of their working capacity after some time. According to Warfield, during the examination of some 40,000 young recruits there were a number of young men with aortic insufficiency who were athletes, some, record holders, who were quite unaware that they had any heart lesions. Cotton (58) states on the basis of observations on soldiers that aortic regurgitation is compatible with health.

Wolf) while the maximum oxygen intake is distinctly lower (Borgard (36)) Only cases compensated for resting condition were investigated by means of this method The decrease of the maximum oxygen intake was proportional to the degree of insufficiency for working condition, i e to the decrease of the circulatory reserve The decrease was especially pronounced in patients with mitral stenosis, where the maximum oxygen intake reached only the value of 200 to 300 cc per minute (Hermannsen (124)) This is only slightly above the resting rate of oxygen consumption In some cardiac patients the maximum oxygen intake was identical with the resting rate (Knipping (158)) so that there was no cardiac reserve at all The rate of maximum oxygen intake is a rather reliable index of cardiac reserve providing no pulmonary complications are involved In the latter case the maximum oxygen intake indicates the capacity of the respiratory and circulatory system If the maximum oxygen intake exceeds a value of 1300 cc per minute, it may be assumed that there is no circulatory insufficiency (Hermannsen (124))

2 *Maximum of Pulmonary Ventilation (Pulmonary Reserve)* The maximum pulmonary ventilation attained during maximum work amounts in the average to 80 liters in male and 50 liters per minute in female normal subjects These values are lower than those obtained by maximum voluntary hyperventilation (100-150 liters, Herbst (119) Simonson (241), Hermannsen (123)) Thus, the pulmonary reserve may be expressed by the difference between the maximum obtained in voluntary hyperventilation and the maximum obtained during muscular work (Marzahn, Gilbeau and Zaeper) The pulmonary reserve in normal subjects diminishes with age, but it exceeds 20 liters in older subjects In normal subjects in good condition as high values as 80 liters have been observed (Hermannsen (123)) Instead of this procedure Knipping (158) proposes to estimate the pulmonary reserve as the difference between the maximum value of lung ventilation obtainable during work and the resting ventilation rate, because the maximum lung ventilation during work is less dependent on the patient's effort than is the maximum voluntary ventilation It may be objected that both maximum voluntary ventilation and maximum muscular effort depend on the patient's cooperation and that by the latter method the total pulmonary reserve is not obtained The difference between the maximum lung ventilation during work and rest in normal subjects may be as high as 94 liters, while it may be as low as 11 liters (maximum ventilation during work 16 liters, resting rate 5 liters difference 11 liters) in patients with emphysema Knipping (156) found a diminution of the pulmonary reserve (i e, a diminution of the maximum lung ventilation obtainable during work) in the following pathological conditions (1) Stenosis in the air passages, produced by carcinoma, enlarged lymphnodes (tuberculosis), bronchitis, asthma, (2) exudate in the alveoli or obliteration (pneumonia, infarct edema, fibrosis silicosis), (3) loss of elasticity of lung tissue (emphysema), (4) alteration of pleura or mediastinum (pleuritic scars, pleuritic exudate, tumor pneumothorax, mediastinal tumors), (5) alteration of the skeletal structure of thorax (6) disease of respiratory muscles and the nervous system (poliomyelitis, phrenic nerve block)

weight, therefore the values should be related to the body weight. As the maximum oxygen intake depends on the minute volume of the heart, a decrease should be expected in cardiac patients. Measuring the maximum oxygen intake is, therefore, an indirect method for determining the maximum minute volume of the heart, providing the pulmonary system is intact. Herbst(121) found a pronounced decrease of the maximum oxygen intake in patients with valvular lesions of the heart paralleling the degree of decompensation. The symptoms of decompensation were slight. Patients with emphysema and chronic bronchitis behaved in similar fashion. In the latter the maximum oxygen intake was diminished more than the pulmonary ventilation. Harrison and Pilcher (110) investigated a type of work (standing-running) near to maximum capacity and found a reduced oxygen intake, especially in patients with mitral stenosis. Buiwell compared cardiac patients with different degrees of functional disability. One of the patients was able to perform exercise comparable to the maximum exercise of the normal subjects, but the oxygen intake during the exercise was less than that of the normals, so that the oxygen debt was greater. In the other patients the maximum exercise, the maximum oxygen intake, and the maximum pulmonary ventilation were much reduced.

Systematic investigations in this direction have been undertaken by Knipping and his collaborators (157-158). Their experimental procedure is as follows. The subject is examined by means of a bicycle or arm ergometer. The ergometer consists of an electrical dynamo. The resistance (and the amount of work calculated in watts) is gradually increased, until the maximum rate of intake of oxygen is reached (Gilbeau, Marzahn and Zaeper) or as long as the subject is able to maintain the speed. This value is reached after two to three minutes, and the work is interrupted after another two to three minutes. The maximum level of pulmonary ventilation is reached one or two minutes after the maximum value of oxygen intake. This occurs in normal subjects at an amount of work equal to 60 to 200 watts, while in heart patients this value is attained between 20 to 30 watts. The gaseous exchange is measured by a closed circuit apparatus, filled with atmospheric air. Oxygen is added at a rate to keep the level of the spirometer constant. Thus the rate of oxygen inflow into the closed circuit system equals the oxygen consumption. Using this arrangement it is easy to see when the maximum oxygen intake is reached. Under these precautions, the oxygen pressure within the system remains nearly constant. This procedure also protects the patient. The amount of work should not be increased beyond the limit established by the maximum oxygen intake. In normal subjects the amount of anaerobic performance may amount to six or seven times the value corresponding to the maximum oxygen intake, i.e., up to a virtual value of 30 liters oxygen per minute (Hill). The lowest normal value of the maximum oxygen intake is one liter per minute established in a large number of normal subjects. Values below one liter must be regarded as pathological. In many cardiac patients, compensated for resting condition with symptoms of insufficiency during work, the oxygen consumption is the same as in normal subjects at light and moderate loads (Zaeper, Haebisch, Craneford and

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2 *Maximum of Pulmonary Ventilation (Pulmonary Reserve)* The maximum pulmonary ventilation attained during maximum work amounts in the average to 80 liters in male and 50 liters per minute in female normal subjects. These values are lower than those obtained by maximum voluntary hyperventilation (100–150 liters Herbst (119) Simonson (241), Hermannsen (123)). Thus, the pulmonary reserve may be expressed by the difference between the maximum obtained in voluntary hyperventilation and the maximum obtained during muscular work (Marzahn, Gilbeau and Zaeper). The pulmonary reserve in normal subjects diminishes with age, but it exceeds 20 liters in older subjects. In normal subjects in good condition as high values as 80 liters have been observed (Hermannsen (123)). Instead of this procedure Knipping (158) proposes to estimate the pulmonary reserve as the difference between the maximum value of lung ventilation obtainable during work and the resting ventilation rate, because the maximum lung ventilation during work is less dependent on the patient's effort than is the maximum voluntary ventilation. It may be objected that both maximum voluntary ventilation and maximum muscular effort depend on the patient's cooperation and that by the latter method the total pulmonary reserve is not obtained. The difference between the maximum lung ventilation during work and rest in normal subjects may be as high as 9½ liters, while it may be as low as 11 liters (maximum ventilation during work 16 liters resting rate 5 liters difference 11 liters) in patients with emphysema. Knipping (156) found a diminution of the pulmonary reserve (i.e. a diminution of the maximum lung ventilation obtainable during work) in the following pathological conditions (1) Stenosis in the air passages, produced by carcinoma, enlarged lymphnodes (tuberculosis) bronchitis asthma (2) exudate in the alveoli or obliteration (pneumonia infarct edema, fibrosis silicosis) (3) loss of elasticity of lung tissue (emphysema) (4) alteration of pleura or mediastinum (pleuritic scars pleuritic exudate tumor pneumothorax mediastinal tumors), (5) alteration of the skeletal structure of thorax, (6) disease of respiratory muscles and the nervous system (poliomyelitis phrenic nerve block)

No pulmonary reserve at all was found in many of the patients, i e., they were not able to increase their pulmonary ventilation beyond the resting rate. Nevertheless, they were not cyanotic in resting condition.

Similar experiments have been performed by Kaltreider and McCann (146) on 20 normal subjects and 28 patients (11 cases of silicosis, 8 emphysema, 2 chronic bronchitis, 2 bronchial asthma, 5 rheumatic heart disease). The maximum minute ventilation obtained in the 20 normal subjects ranged from 49 to 107 liters with an average of 71 liters, close to Knipping's values. The average value of eight cases of pulmonary fibrosis was 46 liters and that of five cases of emphysema only 37 liters per minute. The pulmonary reserve for normal subjects was 63 liters in the average, that of patients with pulmonary fibrosis 36 liters, and of patients with emphysema only 28 liters. In one case of extensive fibrosis it was reduced to 11 liters. In another case of minimal fibrosis the pulmonary reserve was similar to that of the normal individuals. Dyspnea appears when an individual uses more than a certain per cent of his maximum ventilation (Peabody (213)). Kaltreider and McCann found this dyspnea threshold $\frac{(\text{minute ventilation} \times 100)}{(\text{maximum minute ventilation})}$ to be between 46 and 70 per cent in normal subjects (average 59 per cent), and in patients with pulmonary fibrosis the average value was 71 per cent. Similar findings were observed in cases of pulmonary emphysema. The authors found this index for dyspnea more accurate than the expression $\frac{\text{total ventilation}}{\text{vital capacity}}$ proposed by Harrison et al (108, 112) (the maximum lung ventilation was determined in maximum work). In their experiments the normal individuals stopped riding (on the bicycle ergometer) because of muscular fatigue, the patients with pulmonary disorders because of dyspnea. According to Knipping (156) serious dyspnea during work appears only when the maximum pulmonary ventilation is diminished more than 70 per cent. This is further evidence that there is an ample pulmonary reserve in normal subjects not used even in maximum muscular work. In connection with this the results of Drastich, Adams, Hastings and Compère are interesting. They excised considerable parts of the lungs or produced bronchostenosis and atelectasis in dogs by endobronchial application of ammonia. In resting condition there was no deviation of the O_2 , CO_2 , and pH of the blood from normal values, and during exercise (swimming) the only deviation found was a greater increase of pH. These findings suggest that only a pronounced decrease of maximum pulmonary ventilation affects the maximum oxygen intake. On the other hand, Herbst (120) found the maximum oxygen intake in patients with emphysema and advanced bronchitis reduced more than the pulmonary ventilation, this points, perhaps, to secondary cardiac insufficiency. In patients with asthma both pulmonary ventilation and maximum oxygen intake were reduced during maximum performance.

3 Differentiation between Pulmonary and Circulatory Insufficiency As respiratory and circulatory insufficiency are often combined, it is essential to differentiate between them. In uncomplicated heart disease the arterial oxygen

saturation under resting as well as under working condition is normal (see p 403) Hence, an increased oxygen content in the inspired air would not increase the oxygen intake On the other hand, in pulmonary insufficiency the arterial blood is undersaturated with oxygen Hence, an increased oxygen content in the inspired air would produce an increase of the maximum oxygen intake With these assumptions Knipping (154, 156) proposed to measure the maximum oxygen intake (1) in atmospheric air, (2) breathing an air mixture with high oxygen content If the decrease of the maximum oxygen intake is due only to circulatory insufficiency, the value in arrangement (1) would be the same as in arrangement (2) In case of respiratory insufficiency the maximum oxygen intake would be greater in (2) than in (1) The degree of respiratory impairment could be estimated from the difference between (2) and (1) The maximum oxygen intake in (2) would indicate the maximum limit of cardiac performance According to Knipping, this method is much more convenient and gives better results than the direct measurement of the arterial oxygen saturation This probably is due to the fact that slight arterial undersaturation may not be detectable by direct analysis, performed on 1 or 2 cc blood, while the respiratory analysis shows a cumulative effect related to the total amount of circulatory blood of 4 to 5 liters However, several objections may be raised In maximum work, the oxygen intake of normal subjects may be increased when breathing 50 per cent oxygen-air mixtures (Hill Long and Lupton), although the arterial blood is almost completely saturated with oxygen But probably these differences in the normal subject or in a patient with uncomplicated circulatory insufficiency are small compared to patients with arterial undersaturation Another objection is that not in all cases of respiratory insufficiency would the arrangement (1) and (2) provide a measurable difference If the respiratory insufficiency is due to atelectasis or to fibrosis of alveolar septa the arterial undersaturation is produced by mixing of fully saturated blood from the normal parts of the lung with a part of venous blood passing through the atelectatic parts It is clear that breathing high oxygen mixture would not increase the oxygen saturation of that part of the blood flowing through the atelectatic parts, and therefore no increase of the maximum intake of oxygen can result In the other types of respiratory insufficiency Knippings method of differentiation is undoubtedly very valuable and informative especially when one is conscious of the relativity of the values

Knipping (156 159) and Zaeper et al (284) found in more serious cases an "oxygen deficit even in resting condition i e, the metabolic rate was definitely higher when breathing oxygen-rich air The difference paralleled the seriousness of the case and was of prognostic value These respiratory insufficiencies at rest were in many cases not detectable by any other method Knippings method was of considerable prognostic value for the tolerance of collapse therapy in pulmonary tuberculosis It is interesting that even a slight increase of the oxygen content in the inspired air (25 to 30 per cent) was sufficient to discover arterial oxygen deficits

The measurement of the maximum oxygen intake is probably the best method

to measure the cardiac and pulmonary reserve. It is an objective method, although it depends on the patient's cooperation to work with maximum effort. As considerable effort is demanded, it should be restricted to patients fully compensated for resting condition and applied under necessary precautions (Knipping, Hermannsen (124)). The load should not be increased beyond the maximum oxygen intake. Therefore, for many questions the investigation of a submaximum standard type of work is more appropriate.

The maximum capacity for work is certainly diminished in any disease, but besides pulmonary and heart diseases it has been investigated only in hyperthyroidism. The decrease is more pronounced at high speed than at low speed (Herxheimer and Kost (126), Bansi and Grosscurth (12, 16)). The impairment in hyperthyroidism is not due to a diminution of blood circulation or lung ventilation, but to disturbances of oxidative and metabolic processes in the tissues, connected with a low efficiency for muscular work (see Chapters II and III). In the later stages of this disease, however, the circulatory system is impaired, so that in those patients the diminution of the maximum capacity for work is also due to the circulatory system.

4 Maximum Oxygen Debt As another objective method to measure the maximum capacity for work, the measurement of the maximum oxygen debt has been used. Oxygen debt is the excess amount of oxygen consumed during the recovery period (some details of its measurement are discussed in Chapter III, B). The oxygen debt increases with the intensity of work and reaches the highest amount in anaerobic work (of a duration between 10 to 30 seconds) performed with maximum speed or load. The maximum oxygen debt is lower in cardiac patients (Heibst (121), Meakins and Long, Harrison and Pilcher (110)). The latter authors believe that the factor limiting working capacity in patients is the inability to accumulate a large oxygen debt. It is also possible that this failure results from the inability of patients to perform the huge amount of anaerobic work necessary to contract a maximum oxygen debt. It has been shown that accumulation of oxygen debt plays only a secondary rôle in fatigue of normal subjects (Simonson and Sirkina (254)). There is no experimental evidence that in patients the accumulation of the oxygen debt is of greater functional importance than in normals. As the intensity of anaerobic work exceeds that of maximum oxygen intake, the danger of overtaking the patient is much greater. Furthermore, in a given submaximum standard type of work, the oxygen debt is usually greater in patients (see Chapter III). If the same method (measuring of the oxygen debt), applied in different conditions (maximum work and submaximal standard work), gives just opposite indices for evaluation of results, confusion might easily result.

5 Relative Maximum Working Capacity The danger of overtaking the patient with maximum performance induced some authors to investigate a relative maximum capacity, related to symptoms manifest before the absolute maximum is reached. Master and Oppenheimer (185, 186), for instance, using as standard work ascending and descending two steps, gradually increased the number of ascents until the maximum number was reached which could be accomplished

without delaying beyond two minutes the return of blood pressure and pulse rate to resting condition. The maximum tolerance is calculated as foot pounds per minute dependent on age, sex and body weight. It is doubtful whether this method gives more than the measure of recovery processes after a given standard work (see p. 370) and it is more complicated because the work must be repeated several times until the maximum number of steps is established. Proger, Minnich, and Magendantz measured the endurance in hard work (with the bicycle ergometer) in patients with angina pectoris until the appearance of pain. The pain is undoubtedly partially due to anoxemia (Katz et al. (150)), but other less measurable factors are involved too for instance, the different individual sensitivity of the central nervous system. This method cannot be used to compare normal subjects and patients and hardly for comparison of different patients. However, it might be used to show the effect of therapeutic procedures in the same patient. Thus the endurance increased in one patient with angina pectoris from 4 minutes to 9.5 minutes and in another from 4 minutes 50 seconds to 7 to 8 minutes after abolishing the cardiac irregularities by quinidin sulfate.

Similar in this respect are Means and Newburgh's studies: they increased the load until the sensation of "discomfort" was reported. The threshold of discomfort for normal subjects was 1,040 mkg. per minute, that of a patient with mitral and aortic insufficiency only 630 mkg. per minute. This patient was able to do light work without discomfort. We mentioned that the sensation of discomfort is of quite different character in normal individuals and in cardiac patients.

Numerous investigations to establish an index for relative maximum work tolerance have been performed by Barringer and Teschner (18-21). They found that the systolic blood pressure reached the highest value one or two minutes after the work if the work exceeded a certain amount. The amount of work required to call forth this delayed increase of the systolic blood pressure paralleled the individual working capacity. The amount of work where the delayed increase of blood pressure occurred was given in foot pounds. The standard work used was lifting of dumbbells of 3 to 25 pounds each. In patients (19-21) the delayed rise of the systolic blood pressure occurred after much smaller amounts of work while the normal relative capacity was given in thousands of foot pounds, that of patients amounted to only some hundreds of foot pounds. Patients with marked cardiac insufficiency could not do the slightest amount of work without the delayed increase. With the improvement of the patient's condition the amount of work which could be done without the delayed blood pressure rise markedly increased. Barringer and Teschner believe that the delayed blood pressure increase indicates an overtaxing of the left ventricle. There is no evidence for this explanation. The minute volume of the heart drops immediately after cessation of work, in normal subjects as well as in patients. Hence, the delayed blood pressure increase is probably due to disturbance of the peripheral vascular regulation. Barringer's phenomenon has been confirmed by Cotton, Rapport and Lewis. Mann used Barringer's phenomenon

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and found the capacity for the relative maximum work markedly decreased in ten patients in the early stage of convalescence after infectious diseases and an increase with the progressing improvement of the patient's condition. Also Proger et al noticed a delayed increase of the blood pressure in a group of cardiac patients. In Wilson's investigations in 45 normal children and in 116 patients in the age of 6 to 15 years the delayed increase of blood pressure was less consistent and less significant. Probst investigated body bending (20 times in 45 seconds) in 66 cases with mitral regurgitation. None of his patients showed the delayed blood pressure increase, but Probst did not increase the amount of work, so that body bending was perhaps too mild an exercise to produce this phenomenon.

On the other hand, in many patients the heart minute volume drops below the resting value after the exercise, especially in decompensated patients, leading to outright collapse (Bansi and Grosscurth (14, 15)). These observations hardly can be reconciled with Barringer's findings. It may be mentioned that many authors obviously have not noticed this phenomenon, otherwise they would not have failed to mention it. Barringer published his papers in 1915, we were unable to find any references after 1924. A further study of this phenomenon may be interesting.

II DECREASE OF EFFICIENCY (ECONOMY) OF MUSCULAR WORK IN DISEASES

A Methodical Remarks

The coefficient of efficiency is $\frac{W}{Ew - R}$, where W is the amount of work done (calculated as calories, 1 calorie equals 427 m-kilos), Ew the total energy expenditure, R the energy expenditure during rest. Ew and R are computed from the O_2 consumption (indirect calorimetry). There are two methods to determine the coefficient of efficiency. (1) To measure the excess energy expenditure from the beginning of work until the end of recovery and to relate it to the total amount of work done. This method is the only one which can be applied in muscular work of short duration (1 to 7 minutes). The total excess energy expenditure consists of two parts: the energy expenditure (a) during work and (b) during recovery corresponding to the oxygen debt. Since most investigations concern types of work of short duration, this method has been used in the majority of experiments. (2) To measure the excess gaseous exchange per minute during the steady state of oxygen consumption (which is attained after 3 to 5 minutes of exercise) and to relate it to the amount of work done per minute.

In normal subjects there is a fairly good agreement between both methods of calculation (Hill), but this might be due to the fact that the relative importance of the oxygen debt diminishes with the duration of work, so that in a work of 20 to 30 minutes duration, with a steady state of 15 to 25 minutes, variations of the oxygen debt would not alter the coefficient of efficiency considerably.

The oxidative processes responsible for the oxygen debt are probably different

from those during the steady state (Simonsen 246). It is quite possible that these are affected or altered differently by pathological disturbances. Therefore, the method by which the coefficient of efficiency has been determined is important in the interpretation of results. Instead of the energy expenditure in calories, some authors have used the oxygen equivalent per m-hr. As the energy expenditure is calculated from the oxygen consumption, the difference cannot exceed 10 per cent, the limit of variations of the caloric value of oxygen, but it is probably much less. More important is the question of the elimination of the resting metabolic rate. This procedure is complicated by the after-effects of exercise, due to some kind of stimulation of metabolism. In normal subjects this is observed only after very hard exercise, where the metabolism for many hours may exceed by about 10 per cent the resting rate before the exercise (according to Dill 63), however, such stimulating effect is to be assumed also in moderate work. This elevation cannot be regarded as oxygen debt and therefore should not be considered for the calculation of efficiency. In some patients the oxygen consumption may be elevated for a long time after moderate types of exercise, and it is questionable whether this is not a similar process to that observed in normals after hard work. During the recovery period in some patients (especially circulatory insufficiency and obesity, the oxygen consumption frequently sinks below the resting value before the exercise. This negative phase may be observed also in normal subjects, but not so often and not so pronounced. It diminishes the oxygen debt and increases the calculated efficiency, although it often may be regarded as an unfavorable sign. While these difficulties concern the measurement of the energy expenditure, others are involved in the calculation of the amount of work done. Usually only the amount of external work as indicated by the ergometer is calculated, and that amount performed by the movements of legs and parts of the body is neglected, although it may equal or exceed the amount of external work in many types of work (Sebestyen 117).

Due to the difficulties involved in the accurate determination of the coefficient of efficiency, we do not think that differences of efficiency smaller than 10 per cent have any significance if only a small number of subjects are compared. Differences of 25 per cent or more could be considered as significant. It may be mentioned that the coefficient of efficiency is not related to endurance (Simonsen and Sjöholm 252) but reflects another and quite different aspect and index of working capacity.

B. Patients with Heart Disease

In patients with heart disease the results obtained differ according to the type of exercise used and the condition of the patients. In mild exercise of short duration the efficiency was found normal by Campbell and Sale, Campbell

51, Hansen and Picher 119, Rein Sjöholm 151, 258 et al., and Harris and Lyman. The latter authors found in mild exercise a decrease of efficiency in 9 of 17 cardiac patients; in 5 of them the stroke volume was determined and found to be very low during the exercise. In moderate exercise (cycle ergometer

of short duration the efficiency was decreased in patients compensated for resting conditions with some symptoms of decompensation such as some edema in the evening and dyspnea during work (Eppinger and Hinberg (71)), Eppinger, Kisch and Schwarz (72, 74), Laszlo (166, 167)), Zaepfer, Hachisch et al found the efficiency normal in the same type of work in three cardiac patients obviously in better condition than those of Eppinger and Laszlo ("with only slight diminution of working capacity") Bansi and Grosscurth (14, 15) found the efficiency in the same type of work normal in patients with fully compensated valvular lesions and diminished in decompensated patients who were unable to increase sufficiently the minute volume of the heart. The efficiency was normal in the experiments on 11 cardiac patients of Simonson and Gollwitzer-Meier (248). In moderately heavy work (bicycle ergometer) Hermansen (124) found a diminished efficiency in patients compensated for resting condition with some dyspnea during work, while Herbst (121) in a rather hard muscular exercise found the efficiency decreased in fully compensated patients.

This material appears to show that the efficiency does not reflect the primary lesion in cardiac patients. Patients with some light symptoms of decompensation are able to perform light and moderate work with normal efficiency, which seems to decrease only when the symptoms of decompensation are more pronounced. On the other hand, in hard muscular work the efficiency of fully compensated patients may be diminished. The diminution of efficiency is caused only by the increase of the oxygen debt. The oxygen intake during the work is even diminished. In the observations of Harrison and Pilcher (110) (climbing stairs), and of Simonson and Gollwitzer-Meier (248) (genuflexions), the increase of the oxygen debt compensated for the diminished oxygen intake during the work, so that the efficiency related to the total energy expenditure during work and recovery was normal. The increase of the oxygen debt, therefore, is much more consistent and characteristic for cardiac insufficiency than is the decrease of efficiency. The oxygen debt is contracted during the anaerobic period of work. Accordingly, we must conclude that the decrease of the efficiency in patients with heart disease is due to a disturbance of the metabolic processes in the first minutes of exercise, i.e., during the period of adaptation. Simonson et al (240, 245) have shown that the efficiency is low also in normal subjects during this period and improves with the increase of oxygen transportation. The metabolic processes in the beginning of work may be considered as a kind of emergency reaction with low economy. While these unfavorable processes are soon replaced in normal subjects as the work progresses, they seem to be much more pronounced and persistent in patients.

In the steady state of muscular exercise, where an equilibrium between oxygen supply and demand may be assumed, Peabody and Sturges found the efficiency practically the same in 11 normal subjects and 11 cardiac patients (walking in a treadmill). Proger and Korth observed on the bicycle ergometer a coefficient of efficiency of 14.4 per cent in 6 cardiac patients compared to a coefficient of 22.6 per cent in 2 normals. In 3 of the patients the efficiency could be increased by training, so that it equalled the normal values after the training period.

(26 per cent) These authors calculated the efficiency from the steady state of oxygen consumption during the 27th to 30th minute of work They increased the load by one and one-half pounds and calculated the "net efficiency" from the difference of the amount of work at two different loads and the corresponding difference of the oxygen consumption This procedure is discussed on page 361 The different "net efficiency" of patients and normals indicates only that the oxygen consumption increases more in patients than in normals with increasing load, which is quite consistent with the other material discussed The absolute oxygen consumption at the lower load averaged the normal range In the same type of moderate work (234 and 351 m-kilos per minute) the efficiency was normal in investigations of Alt, Walker and Smith on 7 patients and 3 normals One of these cases was described as "advanced aortic insufficiency," but obviously he must have been able to perform the exercise for 25 minutes duration

Material on the fundamental question concerning the deterioration of the economy of muscular work during the steady state in patients with heart disease is scanty It seems quite possible that during the steady state the oxidative processes in cardiac patients are normal when a certain load is not exceeded Many patients with heart disease are certainly able to work with normal efficiency within the limits of the steady state of oxygen intake that they are able to maintain It is known that the basal metabolic rate is increased in many patients with heart disease (bibliography s Altschule) Is there any relationship between the increase of energy expenditure during rest and during work? The increase of resting metabolic rate is to a large degree due to the hyperpnea (Peabody, Wentworth and Barker) The pulmonary ventilation in cardiac patients during work increases more than in normals ((see Chapter V) But the relative importance of this factor for the energy expenditure diminishes as the absolute energy expenditure increases The diminution of efficiency is more pronounced the harder the type of exercise Therefore, pulmonary hyperventilation plays a small, almost negligible rôle in the deterioration of efficiency The same might be said of the efficiency of the heart itself It is known that the efficiency of the hypodynamic heart is diminished The part of the heart in the total energy expenditure during rest is estimated to be between 5 and 10 per cent A change of the efficiency of the heart is within the technical error of the measurement of the gaseous exchange Revers found no relationship between the increase of the resting metabolic rate and the decrease of the efficiency There is reason to believe that the deterioration of efficiency is related to the tissue anoxia We mentioned the parallelism of the decrease of the efficiency to the inability to increase the stroke volume of the heart Loewy, Cohnstamm et al found the efficiency of muscular work 25 per cent and 61 per cent less at an altitude of 2,450 m The diminished economy could be reproduced in experimental acute collapse, where the circulation through the muscles is diminished, leading to oxygen lack in the tissues In Eppinger s (69) experiments on dogs during the pepton and histamin shock, a given amount of work was produced by electrical stimulation of the sciatic nerve, and the oxygen consumption was

greatly increased after a primary drop, so that the efficiency was only one-fourth of the normal value. In circulatory insufficiency there is also a peripheral oxygen lack partially due to the storage of large amounts of blood in the capillaries (backward failure) similar to collapse and partially due to the inability of adequate increase of the heart minute volume (forward failure). The inadequacy of oxygen supply leads to a disturbance of the chemical processes, characterized by increased formation of lactic acid, which is especially pronounced during the period of adaptation. The deterioration of efficiency is generally parallel to the state of the patients, but in patients with slight symptoms of decompensation the efficiency may still be normal, while other functions (oxygen debt, recovery) show distinct deviations. This concerns the comparison of patients with normals and is partially due to the considerable individual variations and technical errors as discussed above. If the efficiency of the same patient is compared in different conditions, it may reflect the patient's condition quite accurately (Blumenthal). The efficiency was improved in patients with angina pectoris after thyroidectomy and by prolonged restricted diet (Proger et al (221)) and after 14 to 28 days treatment with massage in three patients with slight symptoms of decompensation, the improvement of the efficiency was due to the diminution of the oxygen debt (Eppinger and Hinsberg (71)).

The efficiency of muscular work is normal in hypertension (Harris and Lipkin, Gollwitzer-Meier and Simonson (93)).

C Patients with Exophthalmic Goiter

There is complete agreement that efficiency in any type of work is considerably reduced in patients with hyperthyroidism. The increase of energy expenditure for the unit of external work may be more than double the amount in normal subjects. The deviations of efficiency in hyperthyroidism are much greater than in heart disease. Obviously the decrease of efficiency in hypothyroidism is concerned with the fundamental disturbance. Similar observations have been made by Bansı (12), Smith, Herxheimer (126), Thaddea, Zondek, Plummer and Boothby, Kisch, Boothby and Sandiford. The oxygen consumption during work and during the steady state was increased as well as the oxygen debt (Thaddea, Plummer and Boothby, Boothby and Sandiford). The increased metabolism during rest cannot be used for the increased demand during exercise, on the contrary, the conversion of chemical energy into mechanical energy is greatly impaired.

Thyroidectomy leads to a consistent improvement of the efficiency, almost to normal values, while the improvement of the basal metabolic rate was not as consistent (Boothby and Sandiford). The deviations of the coefficient of efficiency precede the alterations of the B M R when the patient's condition improves or becomes worse (Kisch, Boothby and Plummer). In beginning exophthalmic goiter the coefficient of efficiency may be decreased before the B M R is elevated (Zondek, Thaddea).

The coefficient of efficiency more nearly parallels the seriousness of the disease than does the increase of the basal metabolic rate and therefore might be of

considerable diagnostic and prognostic value. Increased production of thyroxin does not account for the increased energy expenditure during work. Formation of thyroxin as well as its action on the oxygen consumption are much too slow and too small in amount to be responsible for the rapidly increased oxygen consumption during work. This does not exclude the possibility that the calorogenic effect of injected thyroxin is increased by a period of training as shown by Boothby, Buckley and Wilhelmj. Their results may be explained by the vasodilatation produced by training so that the injected thyroxin is distributed to a greater surface for its metabolic action. Kommerell (162) tried to find an explanation in another direction. He investigated a dog pulling a load of 2 and of 4 kilos while running in a treadmill. After thyroidectomy the energy expenditure dropped for resting condition between -10 and -17.5 per cent, for working condition -10 per cent for the 2 kilo load and for the 4 kilo load -15.3 per cent. After injection of thyroxin the energy expenditure increased most pronouncedly for the 2 kilo load. The same experiment was carried out (163) on a patient with exophthalmic goiter having a basal metabolic rate of +60 per cent and compared to a normal subject. The subjects had to perform work with the bicycle ergometer at two different loads, equal to an amount of 180 and 360 m-kilos for 4 to 7 minutes. The efficiency calculated from the difference of the two loads was the same in both subjects, although the absolute values were higher in the patient. Hence, Kommerell concluded that the proper or net muscular efficiency is unchanged in exophthalmic goiter, and that therefore the deterioration of efficiency must be due to increased energy expenditure, brought about by deterioration of motor coordination. We believe however, that Kommerell's interpretation of his results is not correct. Kommerell based his investigation on Atzler's (8) scheme that the energy expenditure for the load 0 may be extrapolated from the difference of the energy expenditure between two loads. For a rather wide range of loads the energy expenditure increases in linear relationship to the increase of the load. If the energy expenditure (ordinata) at two different loads (abscissa) is connected by a line, the prolongation of this line crosses the ordinata at the load 0 at a definite point above the abscissa. It is assumed that this value must be the energy expenditure for the same type of movement but without any load, so that alteration of this 0 value must be related to an alteration of the motor coordination. The efficiency calculated according to the formula = $\frac{W_2 - W_1}{E_2 - E_1}$ (W_2 and W_1 = amount of work at two different loads E_2 and E_1 = the correspondent energy expenditure at two different loads) would indicate the proper or net muscular efficiency after elimination of the energy expenditure for the movements of legs and parts of the body. Simonson (243) has shown that the above formula expresses only the increase of the number of stimulated muscle fibers necessary to produce an increased amount of work with increasing load. In this increase the amount for the static component (stabilization of posture) is also included. Kommerell's findings that the inclination of the curve of the energy expenditure with increasing load parallels the normal curve (at higher absolute values) can only be interpreted as indicating that the stimu-

lation of additional muscle fibers with increasing load proceeds in the normal way in exophthalmic goiter, that is, that a fundamental element of motor coordination is not disturbed, quite contrary to Kommerell's own conclusions, based on the change of extrapolated values at zero work. Nevertheless, Kommerell's results are very important. They show that the fundamental disturbance is already demonstrable at small loads, while in heart disease the decrease of efficiency is pronounced only with increasing load. Thus, the same formula of calculation of the "net efficiency" gives different results in cardiac patients, in cardiac patients the "net efficiency" may be decreased although the absolute efficiency at small loads may be normal, but in patients with exophthalmic goiter the "net efficiency" may be normal at greatly diminished absolute efficiency. This would demonstrate the different nature of processes responsible for the deterioration of the efficiency in heart diseases and in exophthalmic goiter. But the results of Kommerell were obtained on only one animal and one patient, so that further investigations in this direction are desirable.

More conclusive are the investigations of Herxheimer and Kost and of Bansi (12). These authors found the decrease of efficiency much more pronounced at high speed than at low speed. The energy expenditure increases with increasing speed in normal subjects due to the viscosity of the muscles (Hill). At high speed a greater amount of energy is necessary to overcome the resistance of the muscle produced by its viscosity. The increase of the energy expenditure occurs at much lower speeds in patients with exophthalmic goiter, and the patients are not able to reach the highest speed values of normal subjects. Herxheimer and Kost classified their 15 patients into three different groups according to the reaction against increasing speed. In the second group the oxygen consumption was normal at moderate speed but higher at maximum speed than that of normal subjects, in the most serious group the oxygen consumption was very considerably increased at the slowest speed and increased still more with higher speed. Bansi's observations are identical. He used (like Herxheimer) stair climbing as standard work. In one typical case with exophthalmic goiter the oxygen consumption per m-kilo was 10.5 when the stairs were ascended in 45 seconds, compared to the normal value of only 2.2 cc O_2 per m-kilo at corresponding speed. After occlusion of the thyroid artery the value for 45 seconds duration of ascending was only 3.3. The pronounced influence of speed on the efficiency in patients with exophthalmic goiter may be explained (1) by increase of the viscosity of muscles, (2) by some physiological processes, where the time factor is essential. It is quite possible that the viscosity is increased. Direct investigations on muscular viscosity are not yet available. The disturbance cannot be due to any circulatory factor, because the minute volume of the heart is not decreased, but increased in exophthalmic goiter as long as no secondary symptoms of circulatory insufficiency occur. Hence, we come to the conclusion that the pronounced influence of speed must be due to change in muscular viscosity or to a diminution of the speed of oxygen diffusion from the capillaries into the tissues or to a disturbance of the speed of those processes which are the link between the liberation and utilization of oxidative energy.

D Patients with Myxedema

We know of only two investigations on the efficiency in patients with myxedema. Bruch compared one child with myxedema with two normal children (between 12 and 14 years). The oxygen consumption during work was less in the patient with myxedema. This would be in agreement with Kommerell's findings on a dog after thyroidectomy. On the other hand, E. Levy found the efficiency normal in patients with myxedema, but they were treated with thyroxin.

E. Patients with Obesity

The efficiency of muscular work has some theoretical interest in obesity. It has not been possible to explain the development of obesity either from a diminution of the basal metabolic rate or by the specific dynamic action of foodstuffs.

If there be a decrease of the metabolic rate during exercise in obese patients the obesity could be explained by the increased efficiency: those patients would need less energy for the performance of muscular work. Gessler (85, 86), indeed, observed in obese subjects an efficiency 20 per cent higher than that of normal subjects. Bansī (12) found no consistent or significant changes of efficiency in obese subjects, but the negative phase (see p. 374) was more frequently observed than in normals, so that the oxygen debt was less. When the total excess oxygen consumption is calculated from the oxygen consumption during work and recovery, as is necessary in work of short duration, the total energy expenditure is indeed more frequently diminished in obese subjects due to the negative phase. These findings may be regarded as partial confirmation of Gessler's results. Wang, Strouse and Morton (271) found the efficiency to be lowest in 27 obese women, higher in 9 normal women and highest in 7 women with underweight of 27.6 per cent. Wang (273) reproduced the same results in another series of experiments. These authors used the bicycle ergometer and measured the oxygen consumption during 3 to 8 minutes exercise, but they did not measure the oxygen debt. The absolute values, therefore, are not correct. But in another study, the same authors (Wang, Strouse and Smith (274)) found the oxygen consumption during recovery after the same standard work higher in overweight and underweight patients. Therefore it seems probable that efficiency of underweight subjects would equal that of normal subjects, while the efficiency of obese subjects would be definitely lower if the oxygen debt be considered. A lower efficiency in obese patients was found also by Alt, Walker, Smith and by Prodger and Dennig with the bicycle ergometer, by Voss with a type of work similar to Knipping's ergostat, and by Lauter and Braumann (without indication of the type of work used). Kommerell (161), also using the bicycle ergometer, found the efficiency of obese subjects in the normal range and no negative phase, contrary to Bansī. It is possible that the different types of work used by the different authors explain to a certain degree the discrepancies of the results. We believe, however, that the discrepancies are probably due to the fact that the symptom of obesity may be the expression and the final result

of quite different metabolic disturbances This is in agreement with the generally accepted view

F Patients with Diabetes

Krogh (165) and Lindhard have shown that efficiency is about 10 per cent lower, when fats are used as fuel for muscular work than when carbohydrates are used Hence, a decrease of efficiency in diabetes must be expected, because the proportion of fat combustion is increased in diabetes during rest and in exercise In nine patients with moderate to serious diabetes Grafe and Salomon found the efficiency decreased, but the decrease showed no relationship to the seriousness of the disease They investigated the steady state in a type of ergometer similar to that used by Knipping Efficiency was decreased in eleven patients with moderate diabetes (controlled with insulin) compared to 45 normal subjects (Simonson and Gollwitzer-Meier (249)) Steward, Gaddie and Dunlop found equal efficiency in patients with diabetes and normal subjects (bicycle ergometer) The condition of their patients was not indicated, but they obviously were in a fairly good condition according to the rather high rate of work they were able to perform Most informative are Alberts' and Dietrich's thorough investigations Their subjects performed a moderately heavy work of 6,000 m-kilos within ten minutes (bicycle ergometer) The coefficient of efficiency of ten normal subjects averaged $19.5 \text{ per cent} \pm 0.66$ at a respiratory quotient of 0.95 The efficiency was calculated from the total amount of work and the total excess oxygen consumption during work and recovery The efficiency of ten patients with diabetes, but without acidosis was slightly less $18.9 \text{ per cent} \pm 0.33$ at a respiratory quotient of 0.91 The proportion of fat in the combustion during exercise was 18 per cent for the normal subjects and 30 per cent for the diabetic patients The slight decrease of efficiency in this group could be fully attributed to the increased proportion of fat combustion, according to Krogh and Lindhard In four diabetic patients with acidosis the efficiency was only $15.3 \text{ per cent} = 0.36$ at a R Q of 0.85, indicating a proportion of fat combustion of 50 per cent The very low efficiency of this group can not be explained alone by the increased proportion of fat combustion The authors investigated four normal subjects with the same standard test, after they had accomplished an exercise of 46,000 to 66,000 m-kilos They had no acetone excretion after this exercise The carbohydrate reserves were reduced, so that the R Q was only 0.84, indicating a proportion of fat combustion of 53 per cent, similar to that in the group of diabetic patients with acidosis Nevertheless, the efficiency of the normal subjects (after severe exercise) was much higher ($18.1 \text{ per cent} \pm 0.25$) On the other hand in normal subjects in hunger acidosis (after 36 hours hunger) the efficiency was as low ($15.8 \text{ per cent} \pm 0.31$) as in the group of diabetic patients with acidosis The R Q in hunger acidosis was 0.87, indicating a proportion of fat combustion of 44 per cent Thus, the authors conclude, the low efficiency in patients with diabetes and acidosis is due to the combustion of low fat acids, which obviously can be utilized for muscular work only with considerable loss of energy For further discussion on the disturbed physiology in diabetes see Chapter V, G

G. Patients with Other Diseases

Efficiency is slightly decreased in patients with chronic *bronchitis and bronchial asthma* (Campbell and Poulton), but the slight difference between normals and patients may be explained by the increase of pulmonary ventilation in patients. According to Brieger in *lung tuberculosis* efficiency is decreased only in advanced cases with manifest pathological alterations. Efficiency is decreased by chronic infections, *colds* may reduce efficiency to half the normal value (Knipping (158)). Simonson and Gollwitzer-Meier (250) found a slight decrease of efficiency in eight patients recovering from influenza. According to Voss infections even of slight degree such as *colds*, diminish efficiency. There is also a decrease of efficiency in *beriberi* (Hayasaka and Inawashiro). Finally it may be mentioned that efficiency in mild or moderate work with the bicycle ergometer was within the normal range during pregnancy (Schroeder and Franz). The authors conclude that mild or moderate work is not injurious in this condition.

III THE SPEED OF OXIDATIVE PROCESSES IN PATHOLOGICAL CONDITIONS (ADAPTATION, OXYGEN DEBT, RECOVERY)

The preceding chapter has been concerned only with the quantity of oxygen consumption. Speed of oxidative processes has been considered only in so far as they influence the efficiency of muscular work.

The speed of oxidative processes is another and important index in the analysis of pathological conditions. It depends on (a) the nature of chemical and oxidative processes in tissues, (b) the speed of oxygen-diffusion from capillaries into muscles, (c) transportation of oxygen by circulating blood, (d) capacity of lung ventilation and speed of oxygen diffusion from lung alveoli into blood.

Speed of oxidative processes during and after exercise may be determined by measuring. (a) the speed of the increase of oxygen consumption during the period of adaptation (the first five minutes of work) (b) oxygen debt (c) recovery speed.

Oxygen debt is contracted during the period of adaptation, so that increase of oxygen consumption during the adaptation period is the fundamental process to which the final oxygen debt is related.

A Period of Adaptation

Increase of oxygen consumption during the period of adaptation is the expression of a complicated integral of metabolic, circulatory and respiratory regulations (Simonson (245)). In the normal increase of oxygen consumption proceeds in a very regular logarithmic curve so that it may be expressed by a simple mathematical formula¹ (Hill Simonson (237)). The type of the curve

¹ The formula is $c = \frac{K}{RK'}(1 - e^{-RK't})$, i.e., the increasing oxygen intake c is assumed to

be the result of the coexistence of one process with constant rate K and another process with increasing rate characterized by the speed exponent RK' , t means time in minutes. With increasing time, the expression $e^{-RK't}$ is approaching the value zero, so that the oxygen intake gradually reaches a constant level (steady state) characterized by the simple proportion K/RK' .

is the same in all types of work, although the constants (used in the formula) are different. Increase of oxygen consumption has been investigated in cardiac patients by Meakins and Long, Campbell and Sale, and Campbell (50, 51). The findings are in complete agreement and show a delayed increase of oxygen intake, carbon-dioxide excretion and pulmonary ventilation. The shape of the curves is entirely different from the curve in normals. The increase proceeds rather slowly and gradually instead of the normal logarithmic curve. This was found in moderate as well as in hard exercise (walking and standing-running Meakins and Long, stepping on and off a block with two different speeds Campbell and Sale).

The deviation of the shape of the curve proves that the regulation of circulatory and metabolic processes in the adaptation period is impaired in cardiac diseases. Christensen, Krogh and Lindhard, and Simonson (255), Teslenko and Gorkin have shown that the capacity for maximum work is increased after the period of adaptation is passed. It might be inferred from these results that the delay and disturbance of adaptation processes in patients account for the decrease of the capacity for maximum work and maximum oxygen intake, at least to a certain degree. Simonson et al. (245) have shown that efficiency during the period of adaptation is low. Therefore, the low efficiency of muscular work in many cardiac patients can also be explained by delayed adaptation. The unfavorable and uneconomical chemical processes, which are replaced in the normal subject after a short period of exercise, are much more persistent in the cardiac patients as a result of the prolonged lack of oxygen supply to the muscles, due to the disturbance of circulatory adaptation processes.

Although in cardiac patients the total oxygen consumption for a given amount of work is frequently increased, it is delayed in time, so that the actual oxygen consumption per minute in cardiac patients does not reach normal values. This reaction might be understood as a compensatory one, it means perhaps less strain for the hypodynamic heart to perform a greater amount of work at a lesser intensity distributed for a longer period of time than to perform a smaller amount of work of greater intensity within a shorter period of time. There is some evidence for this conclusion in experiments performed on the isolated heart (Gollwitzer-Meier (91)).

Most adaptation processes are initiated by nervous impulses. Experiments of Peabody and Sturgis give some evidence that the increase of pulse rate in the beginning of exercise (due to the disinhibition of the vagus tonus) is not impaired in cardiac patients. Usually, the pulse rises shortly before the onset of exercise, when the subject knows that he is about to start. This preliminary reaction was the same in normals and cardiac patients. We believe that the greater inertia of circulatory processes in cardiac patients during the period of adaptation may be explained by (a) slower speed of circulation (bibliography s. Altschule), (b) absolute lower value of minute and stroke volume during muscular work, (c) greater amount of blood volume in cardiac patients (Eppinger (70, 74)²), it is clear that the inertia of the increase of the speed of circulation

* It seems possible that this is a contributing factor to the phenomenon of pulsating columns in capillaries.

must be greater at higher values of absolute blood volume, (d) disturbance of the depot-function, and (e) disturbance of capillary regulation

All of these circulatory functions are closely connected with one another and will be discussed in Chapter IV. It can be seen that the delay and disturbance of adaptation processes in cardiac patients may be as much related to disturbances of the peripheral circulatory processes as to disturbances of the heart action itself.

Campbell and Poulton (48) found in patients with chronic bronchitis and with emphysema that the increase of the CO_2 output and the lung ventilation was much slower in the beginning of exercise compared to normal subjects. There are no investigations on the period of adaptation of the gaseous exchange in patients with other diseases.

B Oxygen Debt

There is general agreement that the *oxygen debt* is considerably increased in patients with heart disease, and that the increase parallels the degree of decompensation symptoms. An increase of the oxygen debt may be found in patients in whom the efficiency is still normal (Harrison and Pilcher (110), Simonson and Gollwitzer-Meier (248)). Increase of the oxygen debt in different types of standard work has been observed by Meakins and Long, Harris and Lipkin, Eppinger, Kisch and Schwarz (72, 74), Eppinger and Hinsberg (71), Herbst (121), Nylin (205-208), Katz, Soskin et al. (151), Campbell (50-51), Zaeper (283), Petersen, Christoffersen and Lindhard, Sutton, Britton and Carr.

Hence, it seems that the measurement of the oxygen debt would be an ideal method to evaluate the state of cardiac patients. The oxygen debt is much easier to measure than the increase of oxygen consumption during work, to which the accumulation of the oxygen debt must be related. There are, however, several complications involved in the measurement of the oxygen debt which make standardization and use for clinical purposes rather difficult. The oxygen debt depends on (a) duration, (b) speed, (c) load, (d) type of work. The absolute amount of oxygen debt increases with increasing duration but often reaches a maximum in the third to fifth minute of work (Simonson and Hebestreit (240)). The relative amount of oxygen debt (percentage of the total excess oxygen in recovery related to the total excess oxygen for work plus recovery) diminishes with increasing duration. However, the decrease of the relative amount of oxygen debt with the duration of work is a rather complicated function and cannot be expressed by a simple mathematical formula (Simonson and Hebestreit (240)). The absolute as well as the relative oxygen debt increases with the speed and load. The increase of the oxygen debt with the speed is more pronounced and more regular than the increase with the load, where it is regular only at loads higher than a certain medium load, the value of which depends on constitutional factors (Simonson and Sirkka (252)). The oxygen debt is different in different types of work, even at the same rate and amount of oxygen consumption. Hence the absolute as well as the relative oxygen debt (in percentage of the total oxygen requirement) are comparable only if the duration, speed, load and type of work are exactly the same. The various authors have worked with different standard types

of work, with different duration, speed and load. Although in their experiments the difference of the oxygen debt between normals and patients is significant for the standard conditions they have chosen, the values for the oxygen debt of the different authors are not comparable.

Therefore a detailed analysis of the material must entail a detailed analysis of the experimental procedure. As the general tendency of the findings is uniform, we do not think that a detailed discussion is necessary. On the other hand, some remarks with respect to general principles may be helpful for the evaluation of the present data and for future investigations. The oxygen debt is the cumulative index for the sum of nonoxidized metabolic products, accumulated during the adaptation period of exercise. It is possible that the oxygen debt arises from mechanisms of quite another nature than those demanding the oxygen consumption during the steady state and that an increase of the oxygen debt does not indicate only a *delay* of the same fundamental oxidative processes, but also a difference in the chemical processes (Simonson (246)). The relative oxygen debt in percentage of the total oxygen requirement expresses its importance for efficiency and its dependence on the amount of work done, to which the total oxygen consumption is closely related. In types of work, where the amount of work done depends on the body weight, the total oxygen debt should be calculated also in per cent of the body weight.

Nylin (205-208) expresses the increased oxygen consumption during the initial period of recovery in per cent of the resting metabolic rate. However, an increased percentage of resting metabolic rate cannot be called "oxygen debt" nor even "relative oxygen debt" since oxygen debt is only related to exercise and not to the resting metabolic rate, furthermore, oxygen debt is an amount and not a rate. The oxygen consumption decreases rather abruptly in the beginning of recovery, therefore, a mean value of the oxygen consumption of the first five minutes of recovery depends not only on the amount of oxygen debt, but also on the rate of decrease. In most serious cases there is a pronounced delay of the decrease, so that the large oxygen debt is manifested rather in a prolonged oxygen consumption at moderately increased rate than in a high level of oxygen consumption in the first minutes after work. Undoubtedly, there is a relationship between the actual oxygen debt and the percentage of increase of metabolic rate, but there is no reason to investigate the indirect function when it is possible to investigate, by the same experimental arrangement, the oxygen debt directly. Nevertheless, Nylin was able to demonstrate the practical value of his procedure for many patients. He has based his method on comparative values of 265 normal persons, but the variations in this normal group are very large. The values of cardiac patients however exceeded the normal range, parallel to the diminution of the working capacity. In some cases of coronary sclerosis the patients showed an increased "relative oxygen debt," where the clinical examination and x-ray examination gave negative results. In some cases of auricular fibrillation and of valvular disease without or with only slight cardiac enlargement the oxygen debt was in the normal range. Nylin used three different speeds of work for the differentiation of the degree of decompensation.

Nylin's procedure has been applied by Sutton, Britton and Cair on a rather large material (16 normal subjects, 29 patients). They also observed a wide range of normal variations. Although there was a tendency towards increased values in patients with increasing degree of decompensation, the values of patients and of normals frequently overlapped and in many patients the oxygen debt at the higher speed was the same as, or only slightly more than, that at the lower speed.

Increased fatigue cannot be related to the *absolute amount* of oxygen debt in normal subjects. There is no evidence that it can be in patients. But there is a direct relationship between the *speed of accumulation* of the oxygen debt and fatigue (Simonson and Sirkina (254)). Meakins and Long's results are most interesting in this respect, they indicate that the accumulation of the oxygen debt proceeds faster in cardiac patients.

Oxygen debt has been found to be increased in chronic bronchitis, emphysema (Campbell and Poulton (48)), more advanced lung tuberculosis (Brieger Knipping (154), Nylin (208)), pronounced silicosis (Nylin (208)), one case of ovarian cystoma with considerable reduction of vital capacity (Nylin (208)), one case of pernicious anemia with a red blood count somewhat over one million in a woman of 65 years of age combined with dilatation of the heart (Nylin (208)).

Wang, Strouse and Smith (274), using a method similar to Nylin's, found the increase of the metabolic rate 15 minutes after work with the bicycle ergometer increased more in obese and underweight subjects than in normals, although the differences were rather slight. Lauter and Baumann found in one obese patient a normal oxygen debt and in another an increased one. According to Proger and Dennig, and to Nylin (208) the oxygen debt is increased in obese subjects. There is also an increase of the oxygen debt in exophthalmic goiter (see Chapter II). In cases of slight diabetes without diminution of working capacity, the oxygen debt is normal (Hetzel and Long (128)), while Simonson and Gollwitzer-Meier (249) found in cases of moderate diabetes, but controlled with insulin, without symptoms of decompensation of circulation, an increase of the oxygen debt. In beriberi the oxygen debt is increased (Hayasaka and Inawashiro). It may be mentioned that Eppinger and Hinsberg (71) were able to reduce the oxygen debt in three patients with slight symptoms of decompensation by systematic massage for two to three weeks, while Hinsberg found an increase of the oxygen debt after application of CO₂ baths. Hinsberg found it difficult to reconcile this divergency, but we do not think that there is a contradiction. the massage improves the capillarity in the muscles, similar to the effect of training, so that the oxygen supply to the muscles is improved. This diminishes the oxygen debt, as does the influence of training, of voluntary hyperventilation (Simonson (241)), and of breathing oxygen-rich air mixtures (Hewlett, Barnett and Lewis). The CO₂ baths improve the capillarity in the skin. Although this decreases temporarily the peripheral resistance, the vasodilatation of the skin vessels interferes with the oxygen supply to the muscles during work and demands an increase of blood volume. A period of rest after CO₂ baths is well justified by Hinsberg's results.

C Speed of Recovery Processes

Oxygen debt reflects the delay of oxidative processes during the adaptation period. The pronounced dependence of oxygen debt on the type and conditions of work makes the calculations of the fundamental function, the speed of oxidative processes rather difficult. Hence, it is desirable to measure the speed of oxidations by a direct method. This can be done by measuring the speed of oxidative recovery processes, that is the speed with which the oxygen consumption during the recovery, or the oxygen debt, diminishes. According to Hebestreit (116) there is a close mathematical relationship between the diminution of oxygen debt and the decrease of oxygen consumption. It is questionable whether the diminution of oxidative recovery speed indicates a delay of oxidative processes during the steady state of oxygen consumption. But there is no doubt that the speed of oxidative removal of waste products is a fundamental function and depends on the integrity of the processes *a* to *d* (p. 365). Oxidative recovery speed, therefore, is a very sensitive index of various disturbances involving any of the processes *a* to *d* (p. 365). It increases with training (Simonson and Riesser (238), Liebenow) and diminishes often in fatigue (bibliography Simonson (244)). Recovery speed may be calculated as (a) absolute time necessary for the oxygen consumption to reach the resting rate before the exercise, (b) percentage of the oxygen debt to the total oxygen debt after a certain time of recovery, (c) percentage of metabolic increase after a certain recovery time, (d) speed exponent. The last method is the best, because the speed of recovery is calculated independent of the absolute amount of oxygen debt, while the results of the other methods will give higher values if the oxygen debt is higher (as it is in most pathological conditions) even if the recovery speed is the same. Yet, many data indicate, even if the speed exponent has not been calculated, that the delay of recovery is not due only to the increased oxygen debt, but also to a reduction of oxidative recovery speed. For instance, in Meakins and Long's experiments the absolute time of recovery was greater in cardiac patients when the absolute oxygen debt equalled that of normals, and the shape of the curves in experiments of Campbell and Sale and of Eppinger, Kisch and Schwarz (74), Bansl and Grosscurth (14) indicates the same. Direct calculations of the recovery speed are given in Simonson's and Gollwitzer-Meier's (248) papers. Table I summarizes the findings of various authors in different diseases.

It can be seen that different pathological processes may delay oxidative recovery. Decrease of the oxygen debt (or oxygen consumption) proceeds very rapidly in the first minutes of recovery, later more gradually. Hill believed that the rapid recovery in the first minutes is due to the oxidative removal of lactic acid within the muscle and the slow recovery speed in the later recovery period to the removal of lactic acid from the blood. Dill (63) believed that the slow recovery process reflects the oxidative removal of lactic acid and the early rapid process the removal of other metabolic products. Both views cannot be maintained (Simonson (246)). Simonson (237) has proposed the following formula to calculate the oxidative recovery

$$RK = \frac{1}{t} \ln \frac{\text{oxygen debt (total)}}{\text{oxygen debt after } t \text{ minutes}}$$

RK is the exponent characterizing the speed of declining oxygen debt, 't' is the time where the recovery period is subdivided for the calculation of RK

TABLE I

DISEASE	OXIDATIVE RECOVERY	AUTHORS
Circulatory Insufficiency	Delayed	Eppinger, Kisch and Schwarz (72, 74)
Circulatory Insufficiency	Delayed	Herbst (121)
Circulatory Insufficiency	Delayed	Meakins and Long
Circulatory Insufficiency	Delayed	Campbell and Sale (49)
Circulatory Insufficiency	Delayed	Harris and Lipkin
Circulatory Insufficiency	Delayed	Katz and Soskin (151)
Circulatory Insufficiency	Delayed	Bansi and Grosscurth (14, 15)
Circulatory Insufficiency	Delayed	Simonson and Gollwitzer-Meier (248)
Nervous Cardiac Disturbances	Normal	Herbst (121)
Arterial Hypertension	Normal	Gollwitzer-Meier and Simonson (93)
Emphysema	Delayed	Herbst (120)
Emphysema	Delayed	Gollwitzer-Meier and Simonson
Emphysema and Chronic Bronchitis	Delayed	Campbell and Poulton (48)
Bronchitis and Bronchial Asthma	Moderately delayed	Herbst (120)
Lung Tuberculosis (more advanced)	Delayed	Brieger
Lung Tuberculosis (more advanced)	Delayed	Knipping and Moncreff (160)
Obesity	Delayed	Wang, Strouse and Smith (274)
Obesity	Normal in 1 patient	Lauter and Baumann
	Delayed in 1 patient	Lauter and Baumann
Exophthalmic Goiter	Normal	Herrheimer and Kost
Exophthalmic Goiter	Delayed	Gollwitzer-Meier and Simonson (94)
Exophthalmic Goiter	Delayed	Bansi (12)
Mild Diabetes	Normal	Hetzel and Long
Moderate Diabetes	Delayed	Simonson and Gollwitzer-Meier (249)
Convalescence after Influenza	Delayed	Simonson and Gollwitzer-Meier (250)
General Exhaustion	Delayed	Simonson and Gollwitzer-Meier
Beriberi	Delayed	Hayasaka and Inawashiro
Pregnancy	Slightly delayed	Schroeder and Franz
Chronic Sulfur Poisoning	Delayed	Simonson and Richter (251)

The interference of the rapid and slow recovery process produces a deviation from the exponential function Hebestreit (116) has shown that the deviation has a typical S-shape, if the diminution of the oxygen debt is plotted with the oxygen debt as logarithmic ordinata and the time in minutes as abscissa. This S-shape was found in any type of work (see Fig. 1). At a certain point the S-

C. Speed of Recovery Processes

Oxygen debt reflects the delay of oxidative processes during the adaptation period. The pronounced dependence of oxygen debt on the type and conditions of work makes the calculation of the fundamental function, the speed of oxidative processes rather difficult. Hence, it is desirable to measure the speed of oxidations by a direct method. This can be done by measuring the speed of oxidative recovery processes, that is the speed with which the oxygen consumption during the recovery, or the oxygen debt, diminishes. According to Hebert (116) there is a close mathematical relationship between the diminution of oxygen debt and the decrease of oxygen consumption. It is questionable whether the diminution of oxidative recovery speed indicates a delay of oxidative processes during the steady state of oxygen consumption. But there is no doubt that the speed of oxidative removal of waste products is a fundamental function and depends on the integrity of the processes *a to d* (p. 365). Oxidative recovery speed, therefore, is a very sensitive index of various disturbances involving any of the processes *a to d* (p. 365). It increases with training (Simonson and Riecker (238), Liebenow) and diminishes often in fatigue (bibliography: Simonson (244)). Recovery speed may be calculated as: (a) absolute time necessary for the oxygen consumption to reach the resting rate before the exercise; (b) percentage of the oxygen debt to the total oxygen debt after a certain time of recovery; (c) percentage of metabolic increase after a certain recovery time; (d) speed exponent. The last method is the best, because the speed of recovery is calculated independent of the absolute amount of oxygen debt, while the results of the other methods will give higher values if the oxygen debt is higher (as it is in most pathological conditions) even if the recovery speed is the same. Yet, many data indicate, even if the speed exponent has not been calculated, that the delay of recovery is not due only to the increased oxygen debt, but also to a reduction of oxidative recovery speed. For instance, in Meakin's and Long's experiments the absolute time of recovery was greater in cardiac patients when the absolute oxygen debt equalled that of normals, and the shape of the curve in experiments of Campbell and Sale and of Eppinger, Kreh and Schwarz (74), Bansi and Groscurth (14) indicates the same. Direct calculations of the recovery speed are given in Simonson's and Gollwitzer-Meier's (248) paper. Table I summarizes the findings of various authors in different diseases.

It can be seen that different pathological processes may delay oxidative recovery. Decrease of the oxygen debt (or oxygen consumption) proceeds very rapidly in the first minutes of recovery, later more gradually. Still believed that the rapid recovery in the first minutes is due to the oxidative removal of lactic acid within the muscle and the slow recovery speed in the later recovery period to the removal of lactic acid from the blood. Dill (63) believed that the slow recovery process reflects the oxidative removal of lactic acid and the early rapid process, the removal of other metabolic products. Both views cannot be maintained (Simonson (246)). Simonson (237) has proposed the following formula to calculate the oxidative recovery:

$$RK = \frac{1}{t} \ln \frac{\text{oxygen debt (total)}}{\text{oxygen debt after } t \text{ minutes}}$$

RK is the exponent characterizing the speed of declining oxygen debt, "*t*" is the time where the recovery period is subdivided for the calculation of RK

TABLE I

DISEASE	OXIDATIVE RECOVERY	AUTHORS
Circulatory Insufficiency	Delayed	Eppinger, Kisch and Schwarz (72, 74)
Circulatory Insufficiency	Delayed	Herbst (121)
Circulatory Insufficiency	Delayed	Meakins and Long
Circulatory Insufficiency	Delayed	Campbell and Sale (49)
Circulatory Insufficiency	Delayed	Harris and Lapkin
Circulatory Insufficiency	Delayed	Katz and Soskin (151)
Circulatory Insufficiency	Delayed	Bansi and Grosscurth (14, 15)
Circulatory Insufficiency	Delayed	Simonson and Gollwitzer-Meier (248)
Nervous Cardiac Disturbances	Normal	Herbst (121)
Arterial Hypertension	Normal	Gollwitzer-Meier and Simonson (93)
Emphysema	Delayed	Herbst (120)
Emphysema	Delayed	Gollwitzer-Meier and Simonson
Emphysema and Chronic Bronchitis	Delayed	Campbell and Poulton (48)
Bronchitis and Bronchial Asthma	Moderately delayed	Herbst (120)
Lung Tuberculosis (more advanced)	Delayed	Brieger
Lung Tuberculosis (more advanced)	Delayed	Knipping and Moncreff (160)
Obesity	Delayed	Wang Strouse and Smith (274)
Obesity	Normal in 1 patient	Lauter and Baumann
Obesity	Delayed in 1 patient	Lauter and Baumann
Exophthalmic Goiter	Normal	Herxheimer and Kost
Exophthalmic Goiter	Delayed	Gollwitzer-Meier and Simonson (94)
Exophthalmic Goiter	Delayed	Bansi (12)
Mild Diabetes	Normal	Hetzel and Long
Moderate Diabetes	Delayed	Simonson and Gollwitzer-Meier (249)
Convalescence after Influenza	Delayed	Simonson and Gollwitzer-Meier (250)
General Exhaustion	Delayed	Simonson and Gollwitzer-Meier
Benben	Delayed	Hayasaka and Inawashiro
Pregnancy	Slightly delayed	Schroeder and Franz
Chronic Sulfur Poisoning	Delayed	Simonson and Richter (251)

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shaped curve crosses the mean exponential function, which appears as straight line when using logarithmic ordinata. If the RK is calculated at this point it would indicate the average exponential speed of the whole oxidative recovery. At an oxygen debt of about 1,500 to 2,000 cc the point where the S-shape crosses the straight line is at about the third recovery minute. If, therefore, the recovery period after a moderate work is subdivided at three minutes, the RK at this point (RK III) will be close to the average recovery speed. In a normal subject, the typical S-shape may be expressed by calculating the RK after 1 (RK I), 2 (RK II), and 3 (RK III) minutes of recovery, in this case there is $RK I > RK II > RK III$. Simonson and Gollwitzer-Meier (248) found that there is an alteration of the shape of the oxidative recovery curve in patients

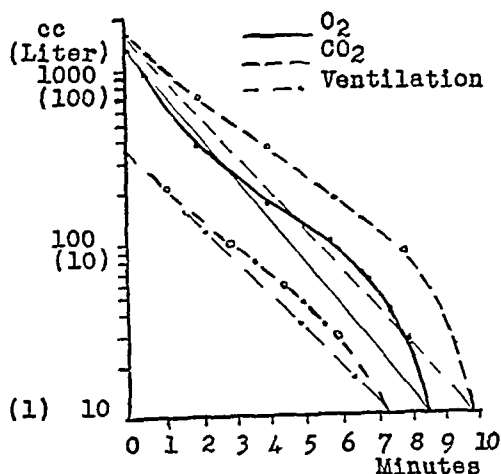


FIG 1 DECREASE OF OXYGEN DEBT, CARBONDIOXIDE EXCRETION AND LUNG VENTILATION DURING THE RECOVERY

Logarithmic ordinata. Decrease of lung ventilation and carbon dioxide excretion appears to be an almost pure logarithmical (straight-lined) function throughout the greatest part of the recovery. The decrease of the oxygen debt shows a characteristic S-shape. It is cut at three minutes by the straight-lined exponential function around which the S-shaped deviation occurs (reproduced from Hebestreit (116)).

with circulatory insufficiency and in patients with emphysema, the normal typical S-shape is lost (besides the decrease of recovery speed) and the decline of the oxygen debt is almost straightlined (in logarithmical paper), i.e., the decrease of the oxygen debt is a pure exponential curve in these cases, consequently $RK I = RK II = RK III$. This result shows that the first quick recovery process depends on the transportation of oxygen from the lungs into the tissues and this has been confirmed by Kramer, Obal and Quensel. Therefore, the first phase of recovery is most delayed in disturbances of the circulatory-respiratory system.

There is reason to assume that the first phase of recovery is the most critical period for the circulatory system: the oxygen demand is almost as high as during work, but the minute volume of the heart diminishes rapidly, because the venous

inflow decreases after the cessation of movements. The heart has to use its own reserve power under the influence of impulses from the central nervous system (Gollwitzer-Meier (89, 90)) to maintain a sufficiently large blood circulation.³ The capillaries in the muscles are still enlarged in number and diameter and this increases the circulatory demand. It may be supposed that the heart of cardiac patients (even of many clinically compensated) and of patients with emphysema (where the right heart is often overtaxed) is often not able to compensate for this critical condition. This unfavorable condition of circulation is reflected also in the deterioration of oxygen utilization during this period (Chapter V). It may be mentioned that breakdown occurs more frequently shortly after exercise than during exercise. That in patients with heart diseases the delay of recovery is most pronounced during the first minutes of the recovery period has been observed also by Campbell and Sale, and by Eppinger. Kisch and Schwarz (the speed exponent, however, was not calculated by these authors).

In exophthalmic goiter, diabetes and convalescence from influenza there was a general decrease of the oxidative recovery speed, but the typical normal S-shape was maintained. In these diseases $RK\ I > RK\ II > RK\ III$, i.e., the recovery was delayed uniformly during the whole period or even more pronounced in the later periods. This has been confirmed for exophthalmic goiter by Bansi (12): he observed a rather rapid decrease of the oxygen consumption during the first minutes of recovery, but the further decrease was very much delayed. It appears to be possible to use the alteration of the shape of the oxidative recovery curve to discriminate between circulatory and metabolic disturbances or to recognize additional circulatory decompensation in exophthalmic goiter and diabetes. The diminution of oxidative recovery speed in exophthalmic goiter must be related rather to a disturbance of chemical processes or of oxygen diffusion from the capillaries into the muscle tissue. In diabetes Simonson and Gollwitzer-Meier (249) found a very high correlation-coefficient of $\rho = 0.88$ (calculated according to Spearman's formula) between the decrease of the oxidation recovery speed and the decrease of the excess RQ of muscular work. The decrease of the excess- RQ during work parallels the gravity of the diabetes (Richardson and Levine). This shows that the decrease of the oxidative recovery speed in diabetes is closely related to the disturbance of the carbohydrate metabolism. It may be mentioned that the RK is generally more decreased in patients with heart disease than it is in patients with diabetes.

The decrease of oxidative recovery speed in chronic sulfur poisoning (251) must be related to the inhibition of the oxidative processes in the tissues, produced by the action of sulfurhydrogen on the oxidative ferment. In connection with this Meleginski's findings are interesting. He found that the time necessary to decolorize methylene blue, which is an oxido-reduction process, was increased in normal pigeons from 15.6 minutes for the normal and 23.0 minutes

³ Whether the decrease of venous inflow and the central stimulation of the heart are mutually compensatory is hard to decide because of the lack of experimental data. This question, perhaps, could be approached by experiments with heart denervation.

for the fatigued muscle to 35.9 and 51.2 minutes respectively in C-avitaminosis. Therefore, a decrease of the recovery speed appears to be possible also in man in C-avitaminosis, due to the diminution of the speed of oxidations in the tissues. It is possible that the delay of the recovery speed in or after infectious diseases might be partially caused by the Vitamin C loss frequently observed in these conditions.

Many authors (Speck, Bansi (12), Maish, Gollwitzer-Meier and Simonson (92), Marks, Jahn) have frequently observed that in normal subjects the oxygen consumption drops below the resting value during the recovery period, although the resting metabolic rate was carefully measured. This negative phase is observed in heart patients even more frequently. It is possible that this phenomenon is a symptom of precollapse, due to the unfavorable conditions for the blood circulation during the recovery as discussed above. The experiments of Eppinger (69) give some evidence for this view, in the first phase of experimental pepton and histamin shock in dogs the minute volume of heart and the oxygen consumption drop far below the resting rate. Herbst (122) also holds this view, he measured simultaneously the minute volume of the heart and the oxygen consumption during the recovery period and found that in many cases a negative phase of the minute volume preceded a negative phase of the oxygen consumption. It is also possible that the drop is due to the action of some metabolic products (Gollwitzer-Meier and Simonson (92)).

During recovery all processes which increased during exercise drop until they reach the resting level. There is no question that the oxidative recovery speed is the most fundamental of these processes, because metabolic, respiratory and circulatory functions are related to oxygen consumption. Therefore, all other recovery processes are delayed too, if the oxidative recovery speed is decreased. This does not exclude the observation that the recovery of ventilation and of carbon dioxide excretion may be more delayed than oxidative recovery speed in heart patients (Peabody et al (215), Harrison and Pilcher (110), Campbell and Sale, M. Campbell (51)). Lung ventilation increases more in cardiac patients than does oxygen consumption, the reasons for this will be discussed later (Chapter V). The pronounced delay of carbon dioxide excretion may be due partially to the disturbance of carbon dioxide storage. Lung ventilation decreases in a rather pure exponential curve, so that it appears as a straight line when a logarithmical ordinata is used. Also the carbon dioxide excretion appears as a rather straight line with a very slight S-shape. Hebestreit (116) found in 29 normal subjects that after the end of exercise the lung ventilation reaches the resting rate first, then the oxygen consumption, and the carbon dioxide excretion last. This relationship was rather constant in normal subjects. In patients, however, this relationship was disturbed, the recovery speed of lung ventilation, of carbon dioxide excretion, and of oxygen consumption may be influenced differently (Simonson and Gollwitzer-Meier (250)). In normal subjects, the pulse rate reaches the resting value much earlier than does the lung ventilation or oxygen consumption. In patients with heart disease the recovery of pulse rate may be more delayed than that of the oxygen consumption. Measuring

the speed of oxidative processes yields objective data in regard to the patient's state, especially in cases with circulatory insufficiency. In many cases a deterioration of the oxidative recovery speed is the only objective datum to substantiate the patient's condition, e g, in convalescence after influenza, when the temperature has become normal and no clinical signs or symptoms of the disease are manifest, the patient may still feel weak and unable to work.

IV THE ALTERATION OF CIRCULATORY FUNCTIONS DURING AND AFTER EXERCISE IN PATHOLOGICAL CONDITIONS

A The Volume of the Heart

Heart volume is the sum of stroke volume and residual volume. While methods have been developed to measure stroke volume, there is no method available for residual volume. Calculation of heart volume by x-ray includes the additional factor of volume of heart muscle. In investigating, however, the same subject at rest and during or immediately after exercise, variations of muscle volume play a minor role compared to the enormous increase of the stroke volume. According to Eppinger (70), the capacity of the normal left ventricle ranges between 150 and 210 cc. Some formulas have been proposed to calculate the size of the heart from x-ray films. According to Liljestrand, Lysholm and Nylin the most accurate formula for the calculation of heart volume is that proposed by Rohrer (1916-1917) and, independently, by Kahlstorf (143, 144) (1932) $V = 0.63 Fa 1 \max$, where V is the volume of the heart, Fa the area of sagittal orthodiagraphy, and $1 \max$ the maximal depth of the transverse orthodiagram. Liljestrand, Lysholm and Nylin, using this formula with teleroentgenograms found that the mean error varied between 4 and 31 cc in 12 normal subjects during rest, but the differences during exercise were much greater. While the error may be considered small with respect to the absolute volume of the heart, it is rather large when related to the stroke volume. Calculation of heart volume by x-ray cannot detect deviations of a few cubic centimeters, but it should reflect the huge increase of the stroke volume, during and immediately after heavy muscular work, which is about three times the resting value (Bainbridge). It is astonishing that this is not the case, and, undoubtedly, the discrepancy between the direct determination of stroke volume and the x-ray investigations is one of the most interesting problems in cardiac physiology and pathology. There is complete agreement among numerous authors that the size of the heart as determined by x-ray diminishes immediately after the exercise (Moritz, Hoffman, H. L. Smith, Kienboeck et al, Selig and Beck, Dietlen and Moritz, d'Agostini, Raab, Jundall and Sjogren, Nicolai and Zuntz, Williamson, Bruns and Roemer, Gordon, Ackermann, McCrea, Eyster and Meek). Reduction of heart size was found in three seconds (Nicolai and Zuntz) and 20 seconds after the work (McCrea, Eyster and Meek), at a time when the stroke volume must have been almost as high as during the exercise. Most of the exercises investigated were very heavy, such as exhausting cycling for 31 hours (Dietlen and Moritz) and marathon running (Gordon). Kaplunowa found reduction of the heart shadow after heavy industrial work.

In the literature referred to, frontal projection was used for the calculation of heart volume. The findings of authors using frontal as well as sagittal orthodiagrams were identical (Zdanski, Paterson and Paterson, Eppinger, Kisch and Schwarz (74), Gottheimer and Kost, Herxheimer (125), Kahlstorf (143), Kahlstorf and Ude, Liljestrand, Lysholm and Nylm). Especially interesting are the investigations of Kahlstorf and Ude, and of Liljestrand, Lysholm and Nylm because they simultaneously measured stroke volume, heart volume (calculated from the x-ray film) was decreased when stroke volume was still high.

There is no doubt that the normal reaction of heart volume immediately after exercise is a decrease, and not an increase as one should expect from direct determinations of stroke volume. Decrease of heart volume after hard exercise may be observed for a considerable time. Decrease of the heart shadow after exercise has been reproduced in dogs by Stewart (263) and by Fahr, Wangenstein and Sperling, pericardiotomized dogs also reacted with diminution of heart volume.

In normal subjects dilatation of the heart after exercise has been observed in only a few exceptional cases. Lipschitz observed a somewhat greater proportion, but two-thirds of his subjects showed reduction of heart size. Williamson found in 38 normal subjects only three who reacted with a slight dilatation of 1 mm, of a group of 57 patients with fully compensated heart lesions 25 reacted with dilatation (of 3 mm), and about the same proportion (4 cases) was obtained in a group of 10 cardiac patients with slight symptoms of decompensation (dyspnea on exertion). Williamson concludes that his results show "the extreme reluctance of the heart to dilate, even if there is some degree of myocardial insufficiency," so that dilatation may be regarded as indicative of serious impairment of the heart muscle. According to Kaplunowa, the heart shadow diminished after heavy industrial work in workers with hearts fully compensated but slightly increased in size. Moderate dilatation always occurred in patients not fully compensated. Similar results were obtained by Kahlstorf (144, 145), after exercise with the bicycle ergometer heart size diminished in normal subjects and in patients with fully compensated valvular lesions, while all patients on the borderline of decompensation showed an increase in heart volume.

In connection with this it might be mentioned that Van Liene observed acute dilatation in dogs, cats, rats, and guinea pigs immediately after exposure to low barometric pressure, paralleling the degree of anoxemia. Whether it may be inferred that the dilatation after exercise is due to insufficient oxygen supply to the heart muscle is open to question.

Because of technical difficulties, only a few observations have been made on heart size during hard muscular work. Eppinger, Kisch and Schwarz, Gottheimer and Kost, and Nylm (205) found no demonstrable change in the size of the heart. Bruns and Roemer observed an increased heart volume in 15 per cent of their cases, a decrease in 25 per cent, and no pronounced variation in 60 per cent. McCrea, Eyster and Meek found an increase of heart volume. A most careful study by Liljestrand, Lysholm and Nylm, who used simultaneous photog-

raphy in the frontal and sagittal direction, disclosed an increased heart volume, parallel to the increase of stroke volume as measured by Grollman's method

After effort the following paradox obtains (a) in normal subjects there is a decrease of the heart size, when the stroke volume is still considerably increased, (b) in patients with heart disease there is an increase of heart size, although stroke volume is smaller than in normal subjects. It has been concluded that in normal subjects the increased stroke volume is produced by a more complete emptying of the heart (Kahlstorf and Uhde). Liljestrand, Lysholm and Nylin concluded that there must be some extra factor that causes the heart to empty itself more completely than before the work. "The fact that this decreased heart volume may be observed for many minutes and even for hours after the cessation of work speaks strongly in favor of some hormonal effect." They believe that the known increased adrenalin output is responsible, adrenalin enables the heart to develop the same amount of energy as before with a smaller diastolic volume than it can without adrenalin. In favor of an additional hormonal factor during and after exercise there is also the fact that the change of the heart volume is much more pronounced in passing from the recumbent position (Nylin (205), average value of 11 subjects 843 cc) to the standing position (average value 574 cc) and here no hormonal factor is involved. The relationship between heart size and stroke volume remains the same (about 12.5) in recumbent and standing position, while it drops to 7.65 after heavy work.

The different reaction in patients with heart disease could be explained (a) by the disturbance of the additional hormonal factor, i.e., adrenalin output, (b) by the disturbance of the contraction mechanism. There is evidence that the adrenalin output is normal in cardiac patients during exercise. The disturbance of the contraction mechanism, therefore, is the remaining explanation. This functional disturbance is in many cases revealed by exercise only. Should this be regarded as decompensation or compensation mechanism? According to the material reviewed, increase of heart size after exercise seems to indicate the loss of contraction power or of elasticity, for it occurs only in cardiac patients, but on the other hand, according to animal experiments, the dilatation might enable the heart to increase its performance. The hypodynamic heart increases its performance with increasing volume up to a certain maximum value (bibliography see Gollwitzer-Meier (91)). After heavy work this mechanism is obviously not used in normal subjects, but possibly in cardiac patients. The experimental results in humans suggest that dilatation after work might be regarded as a sign of myocardial damage. The influence following exercise on the volume of the heart seems to be a valuable though not quantitative method for detecting damage to heart muscle, while a diminution of the stroke volume might be due also to peripheral factors.

B Determination of Stroke Volume

In hard muscular work the minute volume of the heart may reach the enormous value of 40 liters with a stroke volume of 200 cc. It seems impossible that this high value can be produced alone by more complete emptying. There-

fore, some increase of the diastolic volume must occur, at least during work. It is probable that the value of 200 cc is too high. Olmes de Carrasco believes that the maximum minute volume does not exceed 30 liters, and that the difference in the oxygen transportation is balanced by increase of the arterio-venous oxygen difference (utilization). It is known that the arterio-venous difference exceeds 140 cc per liter blood only in exceptional cases, and values higher than 150 cc have not been observed. Thus, we come to the conclusion that a constant error might be involved in the usual determination of the stroke volume.

The methods are direct or indirect applications of the principle advanced by Fick (1870), according to which the blood flow can be calculated from the oxygen intake or carbon dioxide output per minute and the difference of oxygen or carbon dioxide content between arterial and venous blood. Thus Fick's formula is

$$\text{minute heart volume} = \frac{\text{oxygen consumption per min}}{\text{arterio-venous O}_2 \text{ difference}}$$

or

$$= \frac{\text{carbon dioxide output cc per min}}{\text{arterio-venous CO}_2 \text{ difference}}$$

Stroke volume is calculated from minute volume by division with the pulse rate. A direct determination would necessitate a sample of right heart blood. Most methods are based on Bornstein's principle, to determine the rate of absorption of inert foreign gas introduced into the lungs. The best method of this kind is Grollman's acetylene method. All methods are based on the presumption that the oxygen consumption within the lungs due to the metabolism of the lung tissue itself is negligible, and that no metabolic processes beyond the needs of the lung itself take place there. It is clear that that amount of oxygen absorbed within the lung does not have to be transported by the blood stream. There is no direct method that would indicate how much oxygen is transported and how much is used in the lungs. But there is some evidence from chemical investigations that oxidation processes might take place within the lungs, at least during muscular work or similar emergency conditions, where there is a want of oxygen supply. Bohr first suggested the possibility of intrapulmonary oxidations. It may be mentioned that Herxheimer (125), and Gotthelmer and Kost explained the discrepancies between the x-ray findings and the stroke volume determinations by oxidative processes in the lungs. Alpern, Simonson, Sirkina and Tutkewitsch determined simultaneously the lactic acid content of the right heart and arterial blood one-half to four minutes after running on the treadmill, in 18 of 24 experiments on five dogs the lactic acid was lower in the arterial blood, that is, the lactic acid disappeared during the passage through the lungs. Since the fundamental studies by Meyerhof and Hill, it is justifiable to assume that the removal of lactic acid is oxidative. These authors calculated at a Meyerhof-quotient of four that about 10 to 20 per cent of the total oxygen consumption during work may be intrapulmonary. These re-

sults could be confirmed by Simonson (247) in a repeated investigation. The disappearance of lactic acid from the blood after passage through the lungs in high altitude has been observed by Winterstein and Gollwitzer-Meier. Although Gesell, Bernthal, Gorham and Krueger found a disappearance of lactic acid in the lungs during rest, there is no question that this process must have a special functional significance in all conditions where the oxygen supply is inadequate. The maximum amount of oxygen which can be transported by 100 cc blood is 30 mg, while the amount of lactic acid is 100 mg (Knipping (155)). It is therefore quite possible that oxidative processes in the lungs are an important factor in pulmonary and cardiac diseases, although no direct evidence is available. Rosenbaum found the lactic acid content lower in the artery than in the right heart (in dogs) and this difference was increased by anoxemia. It may be mentioned that Binet et al (26, 27) has proved that fats also are oxidized within the lungs. If there are oxidative processes within the lungs, we must expect differences between the minute volume determined by means of Grollman's method and by means of Broemser-Ranke's (40, 41) method during muscular work. Broemser's method is based on quite another principle which can be seen from their formula:

$$\Gamma = \frac{Z Q (P_s - P_d) S T}{D \rho C}$$

where Γ is the stroke volume, Z a constant factor = 0.5, Q is the aorta cross section, $P_s - P_d$ is the blood pressure amplitude, S is the duration of the systole, T is the duration of the pulse, D is the duration of the diastole, ρ is the specific weight of blood, and C is the velocity of the pulse wave.

This means that only physical measurements are necessary, such as velocity of pulse wave, blood pressure, etc., so that no chemical process is involved. It is very difficult to apply this method during muscular work. Yet it has been done by Matthes, who interrupted the work for 10 seconds. No significant alteration of the minute volume would occur in so short a period. The values of the stroke volume as determined by Grollman's and Broemser's method were identical for resting condition, but during work the values determined by means of Grollman's method were considerably higher than those obtained by means of Broemser-Ranke's method. The average deviation was 23.8 cc, at an average value of the stroke volume of 123 cc; this would mean that the stroke volume during exercise calculated according to Grollman, is about 19 per cent too high. This difference, obtained by a quite different approach, is the same as calculated by Alpern, Simonson, Sirkina and Tutkewitsch. The difference obtained by Matthes therefore could be explained by intrapulmonary oxidations, on the other hand their experiments seem to demonstrate that during rest intrapulmonary processes do not play any considerable rôle.

The factor of intrapulmonary oxidations may well influence the results of the determination of the stroke volume by means of Grollman's and similar methods. Since the interference of pulmonary oxidations would tend to increase the values as determined by Grollman's method, a decrease of stroke volume such as usually

found in cardiac patients might still be significant, although the absolute values of the stroke volume might not be correct. There are, however, still some other objections which can be made and have been made against the use of this method in exercise. Grollman believed that his method should not be used in exercise because of the rapid circulation in exercise. Blood already exposed to acetylene would return to the lungs so quickly that the rebreathing period would be much too short to permit any accuracy. Christensen maintained that a rebreathing period of eight to ten seconds is sufficient. Even if this be acceptable in normal subjects, a uniform mixture of gas in so short a period might not be obtained in patients with changes in the lungs due to congestive failure (discussion s. Altschule).

Another presumption of Fick's principle is equality of the stroke volume of the right and left heart. For resting condition, equality of the blood flow in the pulmonary arterial and venous system can be assumed, otherwise serious pulmonary disturbances would occur within a few hours (Gollwitzer-Meier). It is possible that a transitory difference between the flow of blood through the pulmonary artery and vein might occur during the rapid adjustments in exercise. Hochrein and Keller, indeed, demonstrated differences of the blood flow in dogs, using Rein's thermostromuhr method, in various experimental conditions. They concluded that the lungs may serve as a blood depot, similar to the liver or spleen. Sjostrand was able to obtain histological evidence that the lungs function as a blood depot in exercise. His experiments were performed in many species (rats, mice, guinea pigs, rabbits, cats, and dogs), so that it might be safe to generalize. In fact, the diminution of vital capacity (s. Chapter V) after exercise is explained by the greater amount of blood in the lungs, this is, at least, the generally accepted view. We think there is little doubt that the blood content of the lungs may vary in exercise and this factor would interfere with the accuracy of methods based upon Fick's principle.*

The importance of movements on the venous inflow is fairly well established. Hence, the blood flow should be expected to differ in different types of exercise with different types of movements, even at the same rate of oxygen consumption. It should be expected, for instance, that the blood flow in leg movements exceeds that in arm movements, and that the blood flow in dynamic exercise exceeds the blood flow in static exercise. Hansen has collected the data of blood flow reported by various authors and plotted the values of these against the oxygen consumption. The blood flow increased parallel to the oxygen consumption entirely independently of the type of exercise. The values obtained in arm exercises coincided with those in leg exercises, and the values in dynamic work coincided with those of static work. Even the values obtained during electrical stimulation by a procedure used some years ago for treatment and known as "Bergonizing" coincided with those obtained in exercise. Two conflicting conclusions may be drawn: either the movements do not have the importance for blood flow, as generally assumed, or the blood flow, as determined by methods based upon Fick's principle, do not fully reflect the actual changes.

* Also the rapid emptying of other blood depots in the beginning of exercise might interfere with the accuracy of blood flow determinations.

Because of these objections, the values of the minute and stroke volume have perhaps mere relative importance. Still the method might have clinical and practical value if consistent and significant deviations between normals and patients could be demonstrated. As the technical error is rather large (according to Altschule duplicate determinations may show deviations of ± 10 per cent) this can only be done by application of statistical methods. None of the authors have done so. Therefore we tried to do that, but found only the results of Harris and Lipkin suitable. The results of our analysis will be discussed in part C of this chapter. In the studies of other authors either the number of normals or of patients or both were not sufficient, or only average values were communicated. Unfortunately, it was not possible to combine results of different authors using the same method because of differences in the type or standard arrangement of exercise used.

Most authors claim considerable differences of stroke volume between normals and patients. It is quite possible that these differences might be found to be significant so that they could be appreciated or evaluated in connection with future investigations to establish the statistical limits of this method. A report of their results and interpretations follows.

C Minute and Stroke Volume of the Heart

1 Resting Value The variation of the resting value of heart minute volume of normal subjects ranges between 1.9 and 2.5 liters per square meter, Starr, Donal et al. found a still greater range of variation. It is therefore, not astonishing that the values of patients and normals overlap. The general tendency of patients' values is in the direction of diminution (Altschule). The resting minute volume has been found to be useless for the individual patient, obviously because of the wide range of normal values, unless the value obtained is extremely low. Many authors failed to find any consistent relationship between the resting minute volume and the patient's condition (Ernst 1932 (76, 77), Eppinger, Kisch and Schwarz 1927 (74), Harrison, Friedman, Clark and Resnik 1934, Nielsen, Lindhard 1937, Nylin 1933 (205), Meyer 1939, Lundsgard 1916 (179), Harris and Lipkin, Hamilton et al.). Objections have been made against Eppinger's method (Altschule), but the other authors used the acetylene method except Lundsgard who used Krogh's and Lindhard's method. Analyzing the data of various authors, Meyer comes to the conclusion that even if the stroke volume is decreased the degree of diminution is not sufficient to explain the symptoms of insufficiency. Probably we have two entirely different mechanisms of compensation. (a) Enlargement of the diastolic volume. The hypodynamic heart is able to accomplish the same performance only when contracting from an increased (dilated) diastolic volume. (b) Increase of oxygen utilization with decrease of the minute volume of the heart. The oxygen consumption and transportation is the product of both factors, therefore, they may replace one another to a certain degree. Both processes (a) and (b) are at the same time compensation and decompensation symptoms. They do not exclude one another but they tend to be reciprocal. It is clear that this complicated interrelationship cannot be analyzed merely from the absolute amount of the blood

flow, and that therefore there is no consistent relationship between resting minute volume and the patient's condition

2 Response to Exercise in Cardiac Patients Any compensatory mechanism involves the use of circulatory reserves. Increase of oxygen utilization is called upon by the increased demand for oxygen during work as well as for compensation of cardiac insufficiency. Therefore, this mechanism is less available for the increased transportation of oxygen in a patient than in normal subjects. This is illustrated by comparison of the oxygen utilization by a patient with mitral stenosis and a normal subject with increasing amount of work (176) in the bicycle ergometer

Work m-kilos per minute	400	500	620	720	960	1,200	1,440	1,680	
O ₂ Utilization—Patient	108	119	5	131					
O ₂ Utilization—Normal Subject									
(cc per liter blood)					94	110	118	119	131

The oxygen utilization of the normal subject is lower at the 720 kgm performance than that of the patient at 400 kgm, and the same limit of 131 is reached in the patient at 620 kgm and in the normal subject at 1,680 kgm. It can be seen that the patient has exhausted this compensatory reserve at an amount of work about one-third that of the normal subject. This leads to a vicious circle and explains why muscular exercise is a much greater strain for the patient: the increase of circulatory performance during work depends much more on his ability to increase the stroke volume, and this function appears to be impaired. This explains also why determination of minute volume during exercise reveals the capacity and reserve power much better than does the determination at rest. There is complete agreement that the cardiac patient is not able to increase stroke volume to the same degree as the normal subject, even if his stroke volume is within the normal range during rest. He compensates for the inability to increase the stroke volume sufficiently by a greater increase of the pulse rate. Even so, the compensation is not complete, the minute volume, being the product of pulse rate and stroke volume, is smaller in the patient than in the normal subject at the same amount of work of different types or at the same oxygen consumption (Harris and Lipkin, Eppinger, Kisch and Schwarz (72, 74), Alt, Walker and Smith, Bansí and Grosscurth (14, 15), Grosscurth and Bansí (100, 101), Meakins, Dautrebande et al., Lindhard). The failure to increase the stroke volume sufficiently is claimed to be proportional to the degree of insufficiency and decompensation. In experiments of Grosscurth and Bansí normal subjects increased the stroke volume in the given standard work (stair climbing) on the average of about 50 to 60 per cent, while patients with symptoms of cardiac decompensation during work increased the stroke volume only about 10 to 20 per cent. The inability to increase the stroke volume may be revealed even by mild exercise. In Harris' and Lipkin's cardiac patients, the results of which are analyzed p. 385, the average value during work is 87 cc, that of six normals is 142 cc, and that of four patients with hypertension without cardiac decompensation 93 cc. One patient with aortic insufficiency and auricular

fibillation who was considered to be the most serious of all the cases showed no increase of the stroke volume. The minute volume was increased only 25 per cent by the increased pulse rate. It is interesting that the resting value of stroke volume in this patient was normal. Medeiros Dauterbande et al. observed in three of their patients no increase of stroke volume. According to Burwell and Bickel, exercise produces no increase of cardiac output in many patients with chronic constrictive pericarditis. In moderately heavy work with the bicycle ergometer performed at the steady state Grosseruth and Bansi (100, 101) found in normal subjects a decrease in stroke volume and increase of pulse rate when fatigue developed. This was much more pronounced in a patient with fully compensated aortic regurgitation. Thus final decrease of stroke volume and

TABLE II

Minute Volume, Stroke Volume, Pulse Rate, and Oxygen Utilization in Normal Subjects and Cardiac Patients at Increasing Loads (according to L. H. Ford)

LOAD	TIME	OXYGEN CONSUMPTION	MINUTE VOLUME	PULSE RATE	STROKE VOLUME
Normal Subjects					
	REST	cc per min	cc		cc
1	Rest	51	45	63	73
3	335	82	121	168	119
5	470	95	132	168	124
5	570	95	140	158	120
5	620	95	159	157	157
		-88%	-250%	-87%	-88%
Cardiac Patients					
11	Rest	51	40	68	75
3	335	98	112	178	82
5	470	121	123	182	92
7	570	109	137	158	87
7	620	113	150	164	94
		-122%	-306%	-148%	-25%

increase of heart rate could be reduced by digitalis, and his performance increased at the same time.

Comparison with different loads might reveal cardiac insufficiency still better. In investigations by Alt, Walker, and Smith the average stroke volume of three normal subjects was 103 cc. at a performance of 294 m.-kg. per minute and 112 cc. at a performance of 351 m.-kg. Only one patient with mitral insufficiency and stenosis showed similar values. In the other three patients there was no significant difference of the stroke volume between 294 and 351 m.-kg. Most informative are Linchard's investigations because four different amounts of work were compared, bicycle ergometer. The acetylene method was used. Table II shows the comparison of a group of normals and a group of patients.

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Walker and Smith investigated two female patients of 24 and 22 years of age with complete heart block with the bicycle ergometer at 234 and 351 m-kilos per minute. The pulse rate of the first case was 43 at rest; it increased to 72 at 234 m-kilos and 87 at 351 m-kilos. The normal average values of pulse rate were 114 and 124. The stroke volume increased from the high resting value 125 cc to 164 cc at 234 m-kilos, far beyond the normal value of 103 cc, but it decreased to 149 cc at 351 m-kilos. This decrease of stroke volume at increasing work might be regarded as a symptom of fatigue of the heart according to Grosscurth and Bansi as discussed above. In the other patient the resting pulse rate was 32 and the stroke volume was as high as 154 cc, which is comparable to normal values during heavy work. This patient could not increase the pulse rate, it was 37 at 234 m-kilos and 38 at 351 m-kilos. The stroke volume increased to the enormous values of 239 cc at 234 m-kilos and 264 cc at 351 m-kilos. These are the highest values of stroke volume hitherto described. It seems that in patients with complete heart block the increase of stroke volume may compensate for the failure to increase the pulse rate.

2. *Significance of Differences in Stroke Volume and Blood Flow between Normal Subjects and Patients* Harris and Lipkin used Grollman's method in six normal subjects and twelve cardiac patients during rest and exercise. This is about the lowest limit permitting statistical evaluation. By subdividing the patients into a group of six with 'auricular fibrillation' and another group of five with hypertensive heart disease, four of whom were compensated, it is possible to calculate the reaction of the group of eleven patients in regard to stroke volume. The twelfth patient with pancarditis could not be classified for this purpose. We calculated standard deviation (SD), standard error (SE) and significance of differences for blood flow, stroke volume and relative increase of stroke volume (resting value taken as 100). A difference between two mean values might be regarded as significant if it exceeds the expression $2\sqrt{SE_1^2 + SE_2^2}$. In regard to the resting value of blood flow there were no significant differences between normals and patients. The average resting stroke volume was 59.2 cc in normals with a SD of ± 8.73 ; that of patients with auricular fibrillation (50.0) coincided with that of patients with hypertension (50.1). The standard deviation of the whole group of patients was ± 12.03 . The difference of the mean value was 9.2, it did not exceed the expression $2\sqrt{SE_1^2 + SE_2^2} = 10.62$. However the values are rather close. Our calculations for the values in exercise are summarized in Table II a. The standard deviation of blood flow is much higher in patients, especially those of Group B (Group C was in a better state of compensation). The differences of blood flow between Group A, B and C have no statistical significance. It is interesting that the standard deviation of the stroke volume is highest in the normal Group A and smallest in Group B. The difference, especially between Groups A and B, is so large, that a definite reason must be assumed. We think that the large range of variations of the stroke volume in exercise in normals might be due to a different training condition, since it is known (233) that with increasing oxygen consumption trained subjects increase the stroke volume more while untrained subjects increase the

Stroke volume at rest is the same in patients and normal subjects. Patients are not able to increase the stroke volume more than 25 per cent (94 cc), and this value is practically reached at 400 m-kg per minute. Further increase of minute volume is obtained by the increase of pulse rate alone, so that at the moderately heavy work of 620 m-kilos the heart rate is as high as 164. This is almost the limit of maximum increase, so that the performance of 620 m-kg must be very near to the maximum performance for these patients. The difference between the normal and the patients' values increases with the amount of work done. We have mentioned that the oxygen utilization of cardiac patients is higher, this means that the minute volume of the heart is smaller not only with regard to the amount of work done, but also to the oxygen consumption. According to Boothby (32), there is a straight line relationship between the rate of oxygen consumption and the minute volume of heart. Hansen has demonstrated the same. This relationship, however, holds good only at work performed at the steady state and at values of oxygen consumption higher than 700 cc per minute (Bansi and Grosscurth (14)). The constant relationship means that the oxygen utilization is constant beyond the value of 700 cc oxygen consumption per minute. The relationship between oxygen consumption and heart minute volume is undoubtedly a fundamental physiological function. It is shifted in cardiac patients to lower values.

The lesser increase of the absolute minute volume in heart patients during exercise is overbalanced by the delayed recovery time (Bansi and Grosscurth (14)), so that the total amount of work performed by the heart and calculated from the whole integral work and recovery is greater in cardiac patients than in normal subjects. We mentioned that the delayed reaction in time at a lesser absolute increase may nevertheless be regarded as compensation mechanism, it may be easier for the hypodynamic heart to maintain a slight increase for a longer period of time than a greater increase for a shorter period, in spite of the fact that the total amount of work would be greater in the first case. We may, therefore, conclude that the hypodynamic heart does not work at maximum economy, but at the easiest mechanical conditions. The greater increase of pulse rate might be explained in the same way. It is, from the viewpoint of economy, an unfavorable reaction, because the economy of the heart decreases with increasing pulse rate. This means that the heart needs more oxygen for the same amount of work. As the insufficiency of the heart is probably due to peripheral anoxia, this is a typical vicious cycle. But, perhaps, this is the only reaction possible if the stroke volume cannot be increased beyond a very low limit.

3 Response in Patients with Heart Block Investigations on patients with heart block are of deciding importance in the evaluation of the functional significance of the increase of pulse rate. Liljestrand and Zander studied one case of uncomplicated total heart block. The ventricular rate was 50 at rest, it increased to 100 beats during heavy exercise. The maximum value of the stroke volume was 100 cc, the cardiac output increased normally with increasing load up to a value of 16 liters at an oxygen intake of 1,500 cc per minute. Alt,

ume The findings of Bansi and Grosscurth (decrease of stroke volume in fatigue see above) may be regarded as a form of cardiogenic collapse because the drop of stroke volume may be removed after digitalis. A critical drop of the stroke volume has been described by Matthes in a normal subject of 27 years of age. The stroke volume dropped as low as to 11 cc during work with the bicycle ergometer at the moderately heavy rate of 543 m-kilos per minute. The subject was unable to continue. It is interesting that the pulse rate dropped parallel to the stroke volume so that the minute volume dropped to the value of two liters i.e. about half the normal resting value. After some minutes of recovery the values were normal. It is possible that this was a cardiogenic collapse due to fatigue of the heart muscle similar to Grosscurth and Bansi's observations. It is difficult to distinguish cardiogenic collapse from peripheral collapse by the stroke volume alone. Cardiac patients are predisposed to either form of collapse in connection with exercise. Excessive drop of minute volume is especially frequent in the recovery period. In normal subjects the heart is able to compensate for the cessation of movements which favor the venous return of blood flow, by means of its own reserve power. In cardiac patients the insufficiency of the heart muscle during this critical recovery period usually does not lead to outright collapse although there is some inadequacy of cardiac output. In one case of mitral stenosis Bansi and Grosscurth (14) observed a drop of minute volume to 1.2 liters during recovery. These authors regard a pronounced negative phase of cardiac output in patients with heart disease as an ominous sign.

Collapse is sometimes observed in normal subjects after heavy exercise. Athletes may collapse immediately after they have finished a performance. There is deep unconsciousness due to cerebral anemia for a short time, sometimes with retrograde amnesia. The subjects look very pale yet usually they recover their consciousness rather quickly especially if the lower extremities are lifted (Jokl (139)). Nevertheless it is advisable to keep them in recumbent position for a longer period of time otherwise the collapse may recur. Complete recovery takes considerable time. This form of collapse may occur in well trained athletes. It can be provoked by standing position. Mateeff (187-189) called this form of collapse 'orthostatic'. The diminution of stroke volume is accompanied by a decrease of blood pressure and diminution of pulse amplitude. The most probable explanation of this form of collapse appears to be a disproportion between the drop of minute volume after exercise and the readjustment of the dilated capillaries. The collapse may be prevented by bandaging the lower extremities. The risk of vasomotor collapse is much increased after infectious diseases (Jokl (139)) so that athletes should refrain for some time from competitions after infectious diseases even if there are no clinical symptoms. The risk of vasomotor collapse is also increased by high environmental temperature due to the additional dilatation of skin capillaries (Jokl).

According to Schellong (229-230) the vasomotor collapse immediately after muscular exercise is also characteristic of Simmonds's disease (hypophosphis). It can be revealed by rather mild exercise tests (climbing of 50 steps at moderate

heart rate more. The much smaller range of variations in Group B may be explained by the pronounced depression of the upper limit, to which the stroke volume can be increased in patients, as a result of which the possible range of variations is narrowed. The difference of the averages was significant between normals (A) and each group of patients (B or C), between normals (A) and the total group of eleven patients (B and C), and even between the Groups B (in clinically worse condition) and C (in state of better compensation).

Also the relative increase of stroke volume (resting value taken as 100) in Groups B and C was significantly depressed compared to normals. The relative increase in Group C was not significantly greater than in Group B, although the difference almost equalled the expression $2\sqrt{SE_1^2 + SE_2^2}$. It is possible that

TABLE IIa

GROUP	FUNCTION	MEAN VALUE	SD	DIFFERENCE OF MEAN VALUES	$\sqrt{SE_1^2 + SE_2^2}$	SIGNIF- ICANT
a) Six normals	Blood flow	9.97	± 0.955			
b) Six patients (auricular fibrillation)	" "	8.63	± 3.237	a - b 1.34	2.76	No
c) Five patients (hyperten- sion)	" "	8.46	± 1.760	a - c 1.51	1.655	No
				b - c 0.17		No
a)	Stroke volume	141.8	± 32.60			
b)	" "	66.8	± 2.963	a - b 75.0	27.34	Yes
c)	" "	85.0	± 18.85	a - c 56.8	31.78	Yes
				b - c 18.2	16.16	Yes
b + c (11 patients)	" "	75.1	± 16.62	a - (b + c) 66.7	29.20	Yes
a)	Relative in-	239.2	± 48.40			
b)	crease of	143	± 35.98	a - b 96.2	49.24	Yes
c)	stroke vol-	166.6	± 23.66	a - c 72.6	45.36	Yes
	ume			b - c 23.6	24.76	No

further studies in a larger material of groups in different states of decompensation might reveal significant differences.

These calculations show that in Harris and Lipkins' experiments the differences of stroke volume between normals and patients are significant, in spite of the large variations. This material is still too small to allow generalization, but it is encouraging enough to suggest further investigations in this direction.

5 Collapse during or after exercise. Minute volume drops during collapse. An outright collapse is, of course, incompatible with work. Eppinger (69, 75) showed the effect of collapse on exercise by electrical stimulation of muscles in dogs during peptone or histamine shock. In normal dogs electrical stimulation increased cardiac output from 1.82 to 3.10 liters, during shock it did not respond to stimulation and was as low as 0.5 liter. This was, however, not due to cardiac damage, but to dilatation of capillaries and diminution of circulating blood vol-



FIG. 2. CURVES SHOWING THE INCREASE IN THE CIRCULATION RATE PRODUCED BY EXORHITHMIC CENTER, COMPARED WITH THAT PRODUCED IN NORMAL SUBJECTS BY WORK

The values are plotted about the mean curve for the increase in circulation rate, due to work. The upper chart shows the curves for the mean values for the two groups considered, which fall above the mean curve for the increase in the circulation rate, due to work (introduced from Boothby & Hymenon. *Circulation Rate in Center*. Archives of Internal Medicine, Volume 55, 1935)

speed) It appears that some function associated with the hypophysis is essential for the adaptation of the blood pressure and the tonus of the capillaries to muscular exercise Some cases of so-called constitutional hypotension seem to be related to Simmond's disease Such disturbance of vasomotor regulation has been reported improved by preparations of the anterior lobe of the hypophysis A third form of vasomotor collapse occurs 10 to 15 minutes after the cessation of exercise It does not occur when the athletes sit or lie down immediately after the exercise According to Jokl (139), a chemical substance producing collapse must be responsible for this form of "delayed" collapse Another form of collapse in athletes is observed in underwater swimming and in lifting It is obviously due to the Valsalva phenomenon The inclination to this form of collapse can be shown by Burger's procedure, where the subjects are asked to breathe against the resistance of a mercury column of 40 mm for 20 seconds In a group of "asthenic" subjects the systolic blood pressure decreases, although most subjects are able to compensate for the increased intrapulmonary pressure, i e., to maintain the systolic blood pressure Some subjects even collapse during this pressure test It is interesting that after infectious diseases well trained subjects may give asthenic reactions in Bürger's pressure test (Ewig (78)) In female subjects this may occur during the menstruation period (Jokl (139))

6 *Response to exercise in patients with exophthalmic goiter* All pathological conditions hitherto discussed are characterized by a decrease of the minute and stroke volume of the heart The opposite reaction has been observed in exophthalmic goiter, where the minute volume exceeds the normal values at the same level of work or oxygen consumption Consequently, oxygen utilization of the blood is less than in normal subjects The fundamental relationship between minute volume and oxygen consumption is disturbed in the opposite way to that noted in cardiac patients The values of the minute volume of cardiac patients lie below the straight line representing the normal relationship (increase of 88 cc cardiac output per each 100 cc O_2 consumption per square meter surface), the values of patients with exophthalmic goiter lie above this line (see Fig 2 reproduced from Boothby and Ryneerson, Arch Int Med, Vol 55, p 555, Fig 2) Similar results have been obtained by Fullerton and Harrop, Liljestrand and Stenstrom, Boothby and Ryneerson, Zondek, Bansı and Grosscurth (12, 13, 14, 16) The discrepancy between the increase of circulation rate and of oxygen consumption during exercise largely disappears after thyroidectomy, even when the absolute heat production and the circulation rate have not returned completely to average normal values The discrepancy between increase of cardiac output and oxygen consumption is still more striking, when the cardiac performance is calculated as the product of "average blood pressure" times "cardiac output" (Bansı and Grosscurth (12, 14)) This discrepancy seems to increase with increasing work and oxygen consumption, as shown in Table III If the total performance of the heart is calculated from the whole integral work and recovery, the values of the patients exceed eight times the normal values This reaction is characteristic for patients without cardiac decompensation Patients with secondary cardiac decompensation react similarly to "primary" cardiac patients

with mitral lesions showed a greater increase of heart rate than did patients with aortic regurgitation or hypertension. Certain patients with angina pectoris are characterized by inability to increase the heart rate. Atropin increases the pulse rate, but not the capacity for work (Proger et al (221)), so that the failure to increase the pulse rate might be due to an increased vagotonus, perhaps a kind of protective mechanism. The same author found other responses of pulse rate to exercise (bicycle ergometer 185 kgm per minute) in other patients with angina pectoris such as cardiac irregularity shortly before the onset of pain, disappearing after exercise than threadly barely palpable pulse during exercise associated with failure of pulse pressure to increase normally, primary respiratory distress with rapid pulse rate. According to Proger, the various types of responses to exercise indicate that angina pectoris is merely a symptom which may be a manifestation of widely different disturbances in different people. The appearance of extrasystoles during work (type B in Proger's observations) is not necessarily pathological.

The recovery time of the systolic blood pressure after ascending and descending two steps was found to be significant for myocardial damage (Rapport). Barringer (18-21) while he worked out the delayed rise of the systolic blood pressure as a clinical test insisted that neither the diastolic blood pressure nor the pulse rate were of any value. Reisinger too failed to find the results obtained by measurement of blood pressure and pulse rate after the 'two step test' satisfactory. According to Cino cardiac failure does not always manifest changes in blood pressure and blood flow simultaneously. Spohr and Lampert hold the view (on the basis of examination of 300 normal subjects and cardiac patients) that decrease of the systolic blood pressure below the resting value as well as its delayed return after exercise (stair climbing) may be considered indicative of cardiac disturbance. Nevertheless neither the blood pressure alone nor the recovery time of pulse rate alone are suitable methods because 50 per cent of patients show normal reaction. If combined only 26 per cent of the cardiac patients escape the recognition. But when additionally the lung ventilation is measured all patients show pathological reactions. It may be mentioned that the majority of nervous cardiac disturbances show normal response to exercise. Without going into further detail these data may suffice to illustrate the different views of many authors in regard to the diagnostic value of blood pressure and pulse during and after exercise.

The determination of the stroke and minute volume in spite of objections which have been raised shows more striking differences between normals and patients than the determination of the pulse rate or blood pressure. The determination of the pulse rate alone might be valuable for patients with mitral lesions (the increase being evaluated as unfavorable symptom) and in some cases of angina pectoris (the increase being evaluated as favorable symptom). The investigations of Bierring et al on the electrocardiogram are also a very valuable contribution. He increased the load of the bicycle ergometer from 100 to 800 m-kilo per minute during the exercise. In normal subjects the pulse rate increased in linear progression in recovery it returned and became steady

It is interesting that the increase of the minute volume is to be observed in "pre-hyperthyroidism" as the earliest pathological symptom, when the basal metabolic rate is still normal (Zondek)

It would appear that the increase of the circulation rate exceeds that of the metabolic rate. These findings explain the disposition of patients with exophthalmic goiter to circulatory insufficiency and the decrease of maximum working capacity. Those patients attain at moderate work the same increase of cardiac output as normal subjects do at heavy work.

The increase of minute volume and stroke volume was in the normal range in one obese subject in good condition (Alt, Walker and Smith), examined at 234 and 351 m-kilos per minute (Bicycle ergometer). Bansi (12) failed to find consistent deviations in obese patients. On the other hand, Lauter and Baumann found the increase of minute volume as well as of oxygen consumption much more pronounced in obese patients than in normals, but these authors used the discredited ethyl iodide method of Henderson and Haggard. Hayasaka and Inawashiro found in patients with beri-beri an excessive increase of minute and stroke volume during work, but the increase of the systolic blood pressure was

TABLE III

Average Heart Performance of Normal Subjects and of Patients with Exophthalmic Goiter at Increasing Oxygen Consumption (according to Bansi and Grosscurth)

Oxygen consumption, cc per minute	700	850	950	1,050
Average heart performance of normals, meter-kilo	13	15	17	20
Average heart performance of patients, meter-kilo	37	40	43	53
Difference	24	25	26	33

lower than in normal subjects. This can be explained by extreme vasodilatation of capillaries.

During pregnancy increase of minute volume during work is within normal range, but recovery is delayed (Schroeder and Franz).

D Pulse Rate and Blood Pressure

Increase of pulse rate might reflect to a degree the condition of the circulation in cardiac patients. A greater increase in cardiac patients might be expected than in normal subjects for a given exercise compensating for the inability to increase the stroke volume. However, the actual results of various authors do not quite support this view. According to Cotton et al (59), the pulse rate reaches the same level in patients and normals "for a given grade of distress." Nevertheless, there was no consistent relationship between pulse rate and signs of distress. However, the sensation of distress is a different one in patients and normal subjects. Mann found the recovery speed of pulse rate without any significance for the reaction of patients, contrary to Master and Oppenheimer and Meakins and Gunson. Eppinger, Kisch and Schwarz (74) failed to find any consistent relationship between increase of the pulse rate and blood pressure during work and the condition of cardiac patients, although as a rule patients

method) increased during work about 30 mm, reached the resting value within 15 seconds, and then sometimes dropped about 10 to 15 mm below this value. According to the response of the venous blood pressure to exercise, he classified cardiac patients into the following types of decompensation: Type I—fairly compensated, resting value normal, insignificant deviations after exercise; Type II—beginning decompensation, resting value normal or decreased, “decrease” after exercise more pronounced and prolonged (for 10 minutes and longer) than in normal subjects; Type III—clinical decompensation, resting value in the high normal range or elevated, “increase” during and after exercise more pronounced than in normals, delayed recovery (between three to five minutes), then, in most cases drop below the resting value; Type IV—pronounced decompensation, resting value increased, enormous increase after exercise with delayed recovery time (10 minutes and more). The response of the venous blood pressure to exercise was found to be valuable for the detection of venous obstruction in the upper and lower extremities (Veal and Hussey), especially in those cases, where the obstruction was not very pronounced and compensated in resting condition by collateral circulation. In normal subjects the venous blood pressure did not increase more than 10 mm during and after the very mild exercise of squeezing a roll of bandage with the hand 30 to 40 times. In patients with local obstruction of axillary or subclavian veins the venous blood pressure rose steadily during exercise from 50 to 962 mm. A similar test was applied to obstruction of iliac or femoral veins (rising on the toes 20 to 30 times) with similar results.

F Velocity of Blood Flow Circulating Blood Volume

The oxygen utilization of blood depends on the relationship between velocity of blood flow and metabolic rate. During work, the velocity of the central blood flow increases, due to increase of minute volume. The speed is slowed down within the working muscle due to the enormous vasodilatation and at the same time the metabolic rate is increased. Therefore, the arteriovenous oxygen difference of the blood flowing through working muscles increases, the general increase of oxygen utilization (difference between right and left heart) depends on the relative amount of blood which has passed through working muscles. Therefore at the same oxygen consumption a high oxygen utilization indicates a slow circulation rate and vice versa, this, indeed, is expressed by Fick's formula. Therefore, the higher oxygen utilization of cardiac patients during rest and work indicates a slowed circulation speed, and this is still more pronounced during work than at rest (see p. 382).

In patients with hyperthyroidism the utilization is lower at rest and during exercise than in normal subjects, this indicates an increase of the general circulation speed, especially in view of the increased oxygen consumption. Here, the discrepancy is greater during exercise than it is at rest, in some patients there is even a decrease of oxygen utilization during work, while normal subjects always show improvement of oxygen utilization (Bansi and Grosscurth (14, 15). According to Harrison and Pilcher (109), the increase of oxygen utilization

somewhat above the resting value. In four patients with angina pectoris the increase of pulse rate was less and developed at a slower rate, it dropped again when a certain amount of work (400-500 m-kilos) was exceeded. It is possible that this is a sign of anoxemia. Schneider and Clarke investigated the effect of increasing the load (from 2,000 to 10,000 foot pounds) on the pulse rate at simulated altitudes of 10,000 to 25,000 feet. The maximum value of pulse rate and the maximum load which could be attained decreased with the altitude. Furthermore, in Biering's four patients the pulse rate dropped below the resting value in recovery, which he never observed in his normal subjects. The decrease of pulse rate at the maximum load coincided with the onset of pain. In patients with complete heart block the increase of the ventricular rate is a positive sign, the greater the increase in exercise, the less incapacitating are the cardiac symptoms (Gilchrist).

The blood pressure is a rather complicated function, so that the relationship to a single process may be disturbed by the interference of other processes. This, perhaps, explains, at least to a certain degree, the different experiences of different authors. The measurement of the blood pressure is valuable in forms of collapse or pre-collapse during or after exercise. Diastolic blood pressure does not show significant alterations during exercise it remains constant or increases somewhat, after exercise it often drops, due to vasodilatation, which is more persistent than the increase of minute volume. A pronounced drop of diastolic pressure after exercise is a characteristic feature of the vasoneurosis of young people and is due to excessive peripheral vasodilatation (Schellong). This phenomenon may be reproduced in normals by nitrites.

E Venous Blood Pressure

Venous pressure is often increased in cardiac patients. However, the values of normal individuals, compensated cardiac patients, and patients in failure frequently overlap (Altschule, Van Nieuwenhuizen). In many instances, marked signs of failure may be present without alteration in venous pressure. It must be assumed that in these cases extensive dilatation of capillaries compensates to a certain degree for the incapacity of the heart. It might be expected, therefore, that the response of the venous blood pressure to exercise would be more uniform in cardiac patients than the resting values, because additional factors (increase of the minute volume of heart, increase of the intrapleural pressure) are introduced by exercise with the tendency to aggravate the performance of the right heart. Harrison, Harrison, Calhoun and Marsh (108) and Schott (235) found, indeed, that the rise of the venous blood pressure during and after mild exercise is greater and more prolonged in cardiac patients than in normal subjects. Budelman reports considerable and prolonged increase of venous blood pressure in cardiac patients in a type of work with which normal subjects showed only a very slight increase. The most thorough investigations into this question are those by Van Nieuwenhuizen. He used a very mild exercise test (flexion of legs with bent knees) in 25 normal subjects and 250 cardiac patients. In the normals the venous blood pressure (measured with Mortz's and Tabor's

produced by emptying of blood depots. This method gives reliable results in normal subjects and animals in high altitude, during exercise, etc. The methods are based on the difference of the speed of the blood flow between the general circulation and the slow circulation within the blood depots. In the spleen the circulation speed seems to be almost negligible while in the liver and splanchnic depots the speed is somewhat higher; these depots function more as large parallel shunting systems. The disappearance of the dye from the blood stream is certainly to a large degree due to the mixing of the blood in the general fast circulation and the slower circulation within the depots, this has been demonstrated for the spleen (Barcroft Zondek, see Table IV). It may be mentioned that the role of the spleen seems to be less important in human beings, since the maximum capacity of the spleen is only 200 cc (Eppinger (70)). It is clear that the reaction of the blood depots cannot be expected to change the dye concentration significantly after the dye has been mixed with the blood depots. This is the case in Kaltreider and Meneely's experiments who injected the dye solution 40 minutes before the exercise. The decrease of blood volume, which these authors have found during exercise appears to be significant only if the dye concentration during exercise exceeds the initial dye concentration. This, however, is not the case. It may be mentioned that in the later phases of exercise the blood volume diminishes due to a passage of water into the muscle. The measurement of the circulating blood volume is not accurate in patients with congestive heart failure for similar reasons. The mixing of injected dyes is altered because the difference of the speed between the blood flow through the congested organs and the so-called blood depots is diminished. These difficulties have been discussed by Harrison and by Altschule (106). Nevertheless, most authors agree that the blood volume is increased corroborating necropsy findings and observations on capillaries (bibliography see Altschule). As the difference of the speed between the blood flow in the general circulation and the blood depots is diminished in patients with heart disease one would expect that the important function of emptying the blood depots is impaired. Ewig and Hinsberg (79) and Wollheim found, indeed, that the normal increase of blood volume at the beginning of exercise did not occur in cardiac patients. As the patient's condition improved, the response of the blood volume to exercise became normal again. Also Chour found in decompensated patients with heart disease no change of blood volume during exercise. Kaltreider and Meneely found also no change of blood volume during exercise in patients, but they obtained the same results in normals, the reasons for this have been discussed above.

In shock or collapse there is a pronounced and critical decrease in circulating blood volume and the blood depots do not respond to exercise in this condition (Eppinger). Although in both conditions (shock and congestive heart failure) large amounts of blood are stored in dilated peripheral capillaries, there is a significant difference. In congestive heart failure there is a diminished minute volume of the heart combined with increased circulating blood volume, in shock

during exercise in cardiac patients without edema is greater than that of normals, but it is smaller in patients with outspoken edema. Thus, the utilization of oxygen would be diminished by edema, obviously because of the decrease of the speed of oxygen passage through the capillary walls. In this case, the blood flow must increase again, so that a vicious circle would result. These findings, however, could not be confirmed by Weiss and Ellis.

Direct methods have been developed to measure circulation time. The principle consists in measuring the time between intravenous injection of some substance and capillary reaction produced by the substance (bitter or sweet taste, cough, heat sensation, etc.). The only capillary nets which are passed through completely are in the lungs, consequently, these methods measure essentially the pulmonary circulation time. The "time" determined must be considered as near the "average" but not necessarily the "fastest" because it is unlikely that that particle which flows fastest at a given moment will be so at another moment (Blumgart and Weiss, J.). Generally the prolongation of circulation time should parallel the decrease of the minute volume. In patients with pulmonary congestion, however, the vasodilatation in the lungs may exceed that of the organs in the great circuit. In these cases, the prolongation of pulmonary circulation time exceeds the diminution of the cardiac minute volume (Altshule).

Circulation time, circulating blood volume, and minute volume are connected with one another according to Vierordt's formula

$$\text{Circulation time} = \frac{\text{Circulating blood volume} \times 60}{\text{Minute volume}}$$

These factors may alter independently to a certain degree, so that there is no complete or consistent relationship between these three factors (Weiss and Ellis). Increase of minute volume, for instance, is usually accompanied by vasodilatation and increase of circulating blood volume. Nevertheless, there is a certain limit of variations which is not exceeded in normal subjects. Circulating blood volume and minute volume have usually the proportion 1:1, this proportion has been called "circulation quotient" by Wollheim. It is nothing else than the average circulation time divided by 60. This quotient is about 1.06 and is much increased in patients with heart disease (up to 20 and more—Eppinger (70)) due to the increase of circulating blood volume and the diminution of minute volume. This explains why the deviation of the circulation time often exceeds that of the minute volume, because it reflects both factors, minute volume and circulating blood volume. There are two different methods to measure the circulating blood volume: the dye method and the CO-method. Both are similar: the volume of blood is calculated from the concentration of dye or of CO-hemoglobin, after injection or inhalation of a certain amount. The dye method measures the amount of plasma, the CO-method, the amount of red corpuscles. With the onset of muscular work there is an increase of circulating blood volume,

is not replaced by the other blood depots Splenectomized subjects fatigue easily and become dyspneic after short duration of exercise, even if the heart and lungs are normal

G *Electrocardiogram*

Paterson and Paterson found in well trained athletes no significant changes in the electrocardiogram after a marathon race Bierring et al, investigating moderately heavy work (800 meter-kilos) with the bicycle ergometer, found the T-wave normal immediately after work, but it increased during the first minute of recovery, reached a maximum during the second minute of recovery, and then dropped to a lower level than before the work (4th to 6th minute of recovery) In no case of normal persons were isoelectric T-waves, much less negative T-waves observed In four patients with angina pectoris the following deviations could be regularly obtained after the exercise (a) Depression of the S-T interval which was most pronounced immediately after the exercise and then gradually diminished (b) Inversion of the T-wave, which reached the maximum 1.5 to three minutes after the work and lasted for nine to ten minutes Katz and Landt used the four lead electrocardiogram They investigated 20 patients with coronary disease The exercise consisted of raising three pound dumbbells with both hands during three minutes while lying in bed This is a very mild exercise, not comparable with the rather heavy exercise used by Bierring Katz and Landt observed a tendency of the S-T segment to shift in a downward direction The changes in Lead IV were characteristic when they occurred "They became deeper, however, in a few instances the T-wave became smaller In all instances where a change occurred, the most significant alteration was a positive angular movement of the S-T segment, making the angle between the S-T segment and the descending limb of the T-wave more acute" The authors conclude that the use of the effect of exercise on the IV-lead electrocardiogram is a valuable adjunct in estimating the status of coronary circulation Taken all in all, their results are less consistent than those obtained by Bierring, there were no changes of the electrocardiogram in some patients after the exercise Especially, they obviously did not observe the inversion of the T-wave, reaching a maximum two to four minutes after the work Probably the exercise was too mild to produce this sign It may be mentioned that Katz and Landt failed to find any parallelism between the development of anginal pain and electrocardiographic changes Are the alterations after exercise in patients with angina pectoris an anoxic symptom? Benson saw only a very slight and inconstant depression of the T-wave and decrease of the QRS amplitude in healthy subjects up to 20,000 feet altitude It is, however, possible that the lack of oxygen in the heart muscle, produced by exercise in patients with angina pectoris is much more severe than may be obtained by any experimental arrangement in healthy subjects Proger and Korth found in three of six patients with rheumatic heart disease and valvular lesions a slight increase of the P-wave in Lead II, in the other three increase of the T-wave after moderately heavy work with the bicycle ergometer

or collapse both functions are decreased. It seems possible that the increase of the blood volume is a compensatory mechanism in congestive heart failure.

The methods of measuring circulating blood volume are more accurate in conditions where the velocity of the circulation is increased, i e., in patients with exophthalmic goiter. According to Zondek, circulating blood volume is increased in patients with exophthalmic goiter (30 to 40 per cent above normal), so that practically all of the blood is in free circulation. This can be understood, because, according to Vierordt's formula, an increase of minute volume must be, to a certain degree, accompanied by an increase of blood volume, otherwise circulatory disorder would result. Increase of blood volume lags behind the increase of minute volume, therefore the circulation time decreases. As no blood is available for circulatory regulation in the depots, the blood volume does

TABLE IV

Increase of CO Concentration in Blood and Spleen in Normal and Thyroidectomized Rabbits During Rest and Exercise

AUTHOR	DURATION OF BREATHING CO	CONDITION	CO CONCENTRATION	
			Blood	Spleen
	<i>minutes</i>		<i>per cent</i>	<i>per cent</i>
Barcroft	3	Normal rest	23	3
	10	Normal rest	33	7
	15	Normal rest	45	14
	3	Normal exercise	19	17.5
	10	Normal exercise	31	33
Zondek	6	Normal exercise	24	24
	10	Normal exercise	37	33
	15	Normal exercise	47	43
	6	Exercise*	27	3
	10	Exercise*	32	5
	15	Exercise*	48	13

* 4 weeks after thyroidectomy

not change during exercise in patients with exophthalmic goiter. The improvement of the patient's condition is reflected by the reappearance of blood depots.

Zondek demonstrated the opposite disturbance in rabbits two to four weeks after thyroidectomy: these animals were unable to bring the blood stored in the spleen into the general circulation, so that the conditions were similar to normal animals during rest. This is illustrated by Table IV.

The blood stored in the spleen is richer in red corpuscles than is the blood in the general circulation. Therefore, the emptying of the spleen increases the number of erythrocytes in the general circulation. Benhamon, Jude, and Marchionni found in three subjects of 24, 40, and 42 years of age who were splenectomized at the age of five, three, and six years no increase of erythrocytes during work. The authors conclude that in this respect the function of the spleen

B Vital Capacity

Pronounced reduction of vital capacity reduces working capacity (Hurtado, et al (136, 137), Peabody, et al (215)). In less pronounced cases there is only a general and average parallelism between working capacity, patient's condition and reduction of vital capacity. This is obviously due to the ample pulmonary reserve which is not exhausted even by severe exercise in normal subjects. When the vital capacity was less than 70 per cent of the predicted (by the formula of Hurtado and Fray (135)), dyspnea was nearly always produced by moderate physical exertion (Kaltreider and McCann). Wilson and Edwards found in 88 children with heart disease a diminution of vital capacity of -2 per cent in a group with no impairment of muscular activity, in a group with reduction of muscular capacity the diminution was -30 to 50 per cent. For the given individual vital capacity is not an accurate index (Stewart and Jack), and this is emphasized by Knipping and Moncrieff. Vital capacity is diminished after hard muscular exercise in normal subjects, due to the increased amount of blood in pulmonary circulation. In cardiac patients vital capacity may diminish after a moderate exercise which is insufficient to influence that of normal persons (Budelman). Harrison et al (107) found a slight, but not consistent or regular decrease of vital capacity after exercise in eight normal subjects as well as in seven cardiac patients.

C Related Pulmonary Ventilation, Dyspnea on Exertion

The unsatisfactory results obtained by measurement of absolute pulmonary ventilation and vital capacity alone induced several authors to relate both functions to each other in order to obtain a more reliable index for the dyspnea threshold. The idea was that the vital capacity determines to a certain degree capacity for pulmonary ventilation, so that distress must result when total ventilation exceeds a certain proportion of vital capacity. Harrison, Turley et al (112) found that dyspnea in cardiac patients was more closely related to the expression $\frac{\text{total ventilation}}{\text{vital capacity}}$ than to either of these factors alone. In Kaltreider and McCann's investigation none of the individuals complained of dyspnea at values of this coefficient below 40, while at values between 40 and 66 mild dyspnea was noted. None of the normal subjects complained of dyspnea or reached a value of this coefficient higher than 50.0 at the rate of 300 m-kilos per minute. Patients with minimal fibrosis reacted like normal subjects. It may be mentioned that no definite relationship was found between the degree of fibrosis revealed in roentgenogram and the appearance of dyspnea. Although this coefficient seems to be valuable for patients with heart disease and with pulmonary fibrosis, it fails to give reliable results in patients with emphysema. Kaltreider and McCann found the expression $\frac{\text{minute ventilation}}{\text{maximum minute ventilation}}$ to be a more accurate index for all conditions, including pulmonary emphysema. This coefficient expresses the pulmonary reserve (Chapter I).

A Absolute Pulmonary Ventilation

Dyspnea is a characteristic feature of both cardiac and pulmonary disorders. Since dyspnea is a "quality," its evaluation is difficult. Measurement of lung ventilation contributes a good deal to an appreciation of the significance of dyspnea. In cardiac and pulmonary disorders absolute ventilation is increased during rest and exercise (Beddard and Pembrey, Campbell (50), Eppinger, Kisch and Schwarz (72, 74), Harrison, Harrison, Calhoun and Marsh, Harrison and Pilcher (110), Herbst (121), Kaltreider and McCann, Peabody (215) and Sturgis (266), Simonson and Gollwitzer-Meier (248). As a general rule the respirations are shallow but more rapid, thus resulting in an increased minute volume. Dyspnea is not accounted for by "total lung ventilation," since normal subjects are not dyspneic at the same respiratory rate (Engelhard, Harrison, Turley, Jones and Calhoun (112), Peabody, Wentworth and Barker). Furthermore, normal subjects and patients show a wide range of pulmonary ventilation during rest and exercise, so that normal values and those of patients frequently overlap. Nevertheless measurement of pulmonary ventilation is of value in heart disease. Increase of pulmonary ventilation during exercise may be one of the earliest symptoms of cardiac insufficiency, when oxygen consumption and efficiency are still normal (Harrison and Pilcher (110), Zaeper, Häbisch, Crane-fod and Wolf). Such individuals with only slightly reduced working capacity are unable to attain a steady state of pulmonary ventilation at moderately heavy work, demanding an oxygen consumption of 850 cc per minute. At this rate the pulmonary ventilation gradually increases to 50 to 80 liters while in normal subjects the steady state is reached at 28 liters. Therefore, in some cardiac cases pulmonary ventilation during exercise may be more indicative of the patient's condition than oxygen consumption, especially if the ventilation rate with increasing load is investigated. In cardiac patients lung ventilation increases with increasing load more steeply than does the oxygen consumption (Zaeper et al, Häbisch). According to Kaltreider and McCann's curves, increase of lung ventilation with increasing load (300 to 600 m-kilos with the bicycle ergometer) appears to be most pronounced in patients with pulmonary fibrosis, even more than in a group of cardiac patients. With regard to absolute values of lung ventilation at 300 m-kilo, highest values were those of cardiac patients, very close to that of patients with fibrosis, somewhat lower were the values of patients with emphysema and lowest the group of normal subjects. When their 28 patients were divided into four groups (I normal, II dyspnea on severe exertion, III dyspnea on moderate exertion, IV dyspnea on slight exertion), average values of the total ventilation increased accordingly. However, there was considerable overlapping, so that it appears that absolute total ventilation or the quotient $\frac{\text{total ventilation}}{\text{surface area}}$ is only roughly proportional to the degree of dyspnea.

in the respiration air to measure utilization, this is the most convenient procedure when working with an open circuit system as no extra calculation is necessary

Utilization of oxygen in respiration air depends on the relationship between pulmonary ventilation and pulmonary blood flow and is influenced by all factors affecting passage of oxygen from alveoli to capillaries. Utilization is diminished by central hyperpnea because the increase of pulmonary ventilation is not accompanied by an increase of blood flow. Central hyperpnea at rest is a frequent reaction in sensitive and irritable subjects in such cases it has no pathological significance. On the other hand, it is a rather regular feature in convalescents from infectious diseases (Simonson and Gollwitzer-Meier (250)). During exercise the tendency to central hyperpnea is suppressed by the chemical stimulation of the respiratory center. Thus, in convalescents from infectious diseases the utilization of the respiration oxygen becomes normal during exercise.

Utilization of the respiration oxygen increases in most types of dynamic exercise, due to increased blood flow, increased oxygen capacity of the blood and the opening of inactive lung alveoli and blood capillaries. It may be mentioned that oxygen utilization of respiration air has to be distinguished from utilization of blood oxygen (arterio-venous difference) as discussed in Chapter IV. Utilization of respiration oxygen depends on the relationship
$$\frac{\text{pulmonary blood flow}}{\text{pulmonary ventilation}},$$
 utilization of blood oxygen depends on the relationship
$$\frac{\text{metabolic rate}}{\text{peripheral blood flow}}.$$

Both expressions are to a certain degree reciprocal, a retardation of blood flow would diminish utilization of respiration oxygen and increase utilization of blood oxygen. This is the case in cardiac patients.

In cardiac patients utilization of respiration oxygen at rest is low (Herbst (121), Eppinger, Kisch and Schwarz (74), Knipping (160), Simonson and Gollwitzer-Meier (248), Moncreffi, Kaltreider and McCann), due to the diminished speed of pulmonary blood flow. In cases with pulmonary congestion impairment of oxygen passage might be a contributing factor. Another important factor is the shift of the oxygen dissociation curve of the blood which will be discussed later. During exercise the differences between normal subjects and patients with pulmonary or cardiac disease become still more distinct, many cardiac patients are not able to increase the utilization of respiration oxygen, and in many patients the utilization may even diminish during work. Similar results have been obtained by Herbst (121), Eppinger, Kisch and Schwarz (74), Simonson and Gollwitzer-Meier (248), Harrison and Pilcher (110), Kaltreider and McCann, Moncreffi.

Increase of the ventilation equivalent during exercise may be the only symptom of cardiac insufficiency in patients with only slightly diminished working capacity (Zaeper et al (284)). In patients with pulmonary diseases the low utilization of oxygen in respiration air is due to diminution of the contact surface between alveoli and blood. Such patients are able to increase blood flow

No single circulatory, respiratory or metabolic function has been found, to which dyspnea could be consistently related, and there is also no convincing evidence that cardiac dyspnea is due to chemical effects on the respiratory center (Christie) Christie and Harrison (106, 111) emphasize the importance of the nervous factor in the production of dyspnea. We feel that any approach to the development of methods for measuring dyspnea thresholds must include a consideration of the central nervous system. There is some evidence (Simonson (244)) that the subjective sensation of fatigue is brought about by a disturbance of the normal relationship between strength of voluntary impulses necessary to accomplish a certain amount of work and the external work. In fatigue the strength of impulses increases and the rate of work diminishes. In a similar way dyspnea might be the result of the disturbance of the normal relationship between the strength of respiratory impulses necessary to produce sufficient lung ventilation and the effect of lung ventilation (blood aeration). The disturbance is due to a relative increase of nervous impulses necessary for the ventilation demand. Disturbance of this relationship might occur in patients at the same ventilation rate as in normals if the same amount of lung ventilation is not sufficient to produce the same aeration. This relationship is also disturbed when the patients have to ventilate more for the same amount of external work or of oxygen consumption. The strength of inspiratory or expiratory impulses, necessary for a certain effect of lung ventilation, may be disturbed by action on the respiratory center, by reflexes from the lungs, by paralysis of respiratory muscles, by fixation of the chest, by the volume and speed of the blood flow, by the composition of the blood, etc.

D Utilization of Oxygen of Inspired Air

Ventilation is subordinated to the transport of oxygen and carbon dioxide, and therefore should be related to these functions or to the total metabolic rate in order to evaluate its physiological significance. Simonson (239) attempted to do this with his "caloric ventilation quotient" ($K V Q$) which represented the minute volume of respiration per calories used. For work and recovery, an excess— $K V Q$ was calculated from the excess lung ventilation and excess energy expenditure. This quotient is reciprocal to utilization of oxygen in respiration air, it was found to be decreased (i.e. utilization increased) by a period of training for several months (Simonson) and increased during chronic sulfur poisoning (Simonson and Richter). As energy expenditure parallels oxygen consumption, ventilation may be related also to oxygen consumption. The formula devised by Anthony
$$\frac{\text{minute volume} \times 100}{\text{oxygen consumption cc per min}}$$
 is similar to the $K V Q$ and expresses the same function. It has been used by Knipping, Moncreiff, Kaltreider and McCann (160). Herbst (119) used as "utilization coefficient" the amount of oxygen retained by the body out of one liter of inspired air. This is nothing else than the oxygen deficit in the respiration air, i.e. the difference of the oxygen content between inspiration and expiration air, corrected for volume. Simonson and Gollwitzer-Meier (248) preferred the oxygen deficit

Knipping and Moncrieff found the ventilation equivalent increased (= utilization decreased during exercise) in four patients with anemia. The results in patients with pulmonary tuberculosis were not uniform. Brieger found marked increase of pulmonary ventilation in more advanced cases of lung tuberculosis. The less uniform results in these cases is obviously due to the ample pulmonary reserve (see Chapter I). Boehme's results corroborated these findings in patients with advanced silicosis: there was a considerable increase of pulmonary ventilation examined in three types of work (genuflexions, stair climbing, bicycle ergometer) while patients with moderate silicosis often showed normal values. Utilization is increased in bronchial asthma (Herbst (120)) due to decrease of pulmonary ventilation while the circulation rate is about normal. These results could be reproduced in normal subjects by introduction of artificial bronchostenosis. In these conditions increased utilization of respiration oxygen is the only way to obtain the necessary amount of oxygen at diminished volume of respiration.

According to Prodger and Dennig, respiratory minute volume is also excessively increased during work in patients with obesity and similar observations have been made in patients with myxedema by Bansi and Grossecurth (16). These authors believed that this is due to an impairment of the passage of oxygen through the alveoli. It is known, however, that the speed of pulmonary blood flow is diminished in patients with myxedema (Blumgart et al (30)) so that it may be related also to a circulatory factor. CO_2 concentration in respiration air shows a similar increase during work and decrease during recovery as does O_2 deficit, although somewhat less pronounced (Simonson and Gollwitzer-Meier (248-250)). Therefore similar findings may be obtained and have been obtained in regard to CO_2 concentration: cardiac patients are not able to concentrate CO_2 in expiration and alveolar air as much as normal subjects do and this is especially pronounced during exercise and recovery (Campbell and Sale). Similar results have been obtained in obese patients by Bansi, Grossecurth and Weigel. This is due to the same factors as diminution of oxygen utilization in respiration air and additionally to diminution of blood CO_2 combining power in cardiac patients (Eppinger, Kisch and Schwarz (74), Schmitz and Preston; further bibliography see Altschule).

E. Oxygen Saturation of Arterial Blood

Arterial oxygen saturation at rest is about 94 per cent; it increases slightly during moderate exercise due to the dilatation of pulmonary capillaries and the increase of active alveolar surface (Himwich and Barr). If the exercise is continued to exhaustion, oxygen saturation might diminish. Eppinger, Laszlo and Schurmeyer (75) found in cardiac patients at rest that the arterial oxygen saturation is within normal limits or only slightly decreased. In patients with chronic pulmonary disease, acute severe pulmonary edema or acute pneumonia there was a marked decrease of arterial oxygen saturation, but many patients with marked pulmonary congestion had normal arterial oxygen saturation. Although there is a general tendency to decreased arterial oxygen saturation in

during exercise, therefore they are able to increase the utilization of respiration oxygen during exercise as long as no cardiac decompensation is involved. In pulmonary patients decrease in utilization of oxygen in respiration air during work is apt to indicate secondary cardiac involvement.

Simonson and Gollwitzer-Meier (248-250) investigated oxygen utilization of respiration air throughout the whole duration of exercise, comparing 40 normal subjects in 78 experiments with groups of patients with heart disease, hypertension, diabetes, exophthalmic goiter, and convalescents from influenza. The exercise of genuflexions was subdivided in succeeding periods of 20 seconds, the recovery in periods each of one minute. Utilization increased at the twentieth second and reached a maximum at the end of the exercise. In the beginning of work the blood flow is increased rapidly by the emptying of blood depots and the favoring influence of movements on the venous inflow, while the chemical stimulation of respiration needs some time to develop. In the first recovery minute utilization of respiration oxygen is as high as at the end of the exercise, then it drops rapidly and is lower during the second and third recovery minute than before the exercise. During the fourth to tenth recovery minute it is still somewhat lower than before the resting value, which is reached in the eleventh to the fourteenth recovery minute.

During the second and third recovery minute the venous inflow decreases rapidly after the cessation of movements, while the lung ventilation is high because the chemical stimulation of the respiratory center is as strong as it was during exercise and maybe greater, since the blood lactic acid continues to increase after exercise, it reaches the maximum in this type of work in the second to third recovery minute (Gollwitzer-Meier and Simonson (92)). This explains the diminution of utilization of oxygen in respiration air during the early period of recovery. These authors found that the difference between normal subjects and cardiac patients is most pronounced during this period, although oxygen deficit in respiration air is lower in patients at any time during work and recovery. Oxygen deficit, determined during the early phases of recovery, is more decisive than the calculation of the ventilation equivalent or the average utilization for the whole period.

In patients with exophthalmic goiter utilization of respiration oxygen is the same and often higher than in normal subjects during rest as well as during exercise and recovery (Gollwitzer-Meier and Simonson (94), Knipping and Moncrieff), this can be explained by the increase of the circulation rate in such patients (see Chapter IV). In diabetes (249) the oxygen deficit may be low or increased, compared to normal values, during exercise and recovery. Two factors are probably responsible, one acting in the direction of increased utilization, the other in the opposite direction. The first factor is probably the diminished CO_2 production in diabetes. Accordingly, the chemical stimulation of the respiratory center and the increase of pulmonary ventilation is less in diabetics. The factor responsible for the decrease of the oxygen deficit in respiration air is not clear, it is possible that this is an early symptom of secondary cardiac insufficiency, which is manifest in the more advanced cases.

mechanism to improve the oxygen supply to the tissues. A characteristic feature of heart disease is tissue anoxia, even though the arterial oxygen saturation is adequate. While the shift of the oxygen dissociation curve to the right improves the peripheral oxygen supply, it makes oxygen saturation in the lungs more difficult. A higher oxygen tension in the alveoli is necessary to accomplish the same saturation. This explains the hyperventilation in cardiac patients, hyperventilation produces a higher alveolar oxygen tension. Therefore hyperventilation in cardiac patients is a necessary compensatory mechanism (Knipping (156), Zaeper (283)). It is quite possible that arterial oxygen under-saturation in cardiac patients with acidosis is also due to the shift of the oxygen dissociation curve and not only to pulmonary congestion. The dissociation curve is shifted to the left in advanced cases of pulmonary tuberculosis (Zaeper (283)). This favors the ease of oxygen saturation in the lungs, so that it must be regarded as a compensatory mechanism for respiratory insufficiency which is the primary disturbance in these cases. As long as there is no secondary cardiac insufficiency the oxygen demand of the tissues may be met by increased blood flow. It can be seen that secondary anemia in pulmonary tuberculosis is a serious complication and will diminish working capacity. It can only be compensated for by a greater circulatory performance. The elevated pulse rate in this condition decreases when breathing oxygen-rich air mixture. On the other hand, increase of the Hb-content as a compensatory mechanism has been observed not only at high altitude, but also in emphysema, asthma, and tuberculosis. During muscular exercise the oxygen dissociation curve shifts to the right in patients with pulmonary insufficiency. This means a disturbance of the compensating mechanism developed (shift to the left), so that the oxygen saturation in the lung is still more impaired. This might explain the oxygen under-saturation of arterial blood, the excessive increase of pulmonary ventilation and dyspnea in these cases during exercise.

According to Knipping, shift of the oxygen dissociation curve to the left in pulmonary insufficiency at rest is an indication that the tissue oxygen supply is sufficient. However, if the arterial oxygen under-saturation is too pronounced or the circulatory system not able to compensate for this, peripheral acidosis occurs, and the oxygen dissociation curve shifts to the right as in exercise. This shift must be regarded as an unfavorable sign, indicative that the limit of adequate peripheral oxygen supply has been reached. In pregnancy there is a shift of the oxygen dissociation curve to the right and this shift is especially pronounced during exercise. This explains the hyperventilation during exercise and the dyspnea, which is not seldom observed in pregnancy (Borgard and Effkemann).

According to Zondek and to Bansi (12) in exophthalmic goiter there is a shift of the oxygen dissociation curve to the right at rest, as in normal subjects during exercise and this shift is more pronounced during exercise as compared with normal subjects. On the other hand the oxygen dissociation curve is shifted to the left in patients with myxedema. In patients with myxedema the left shift (meionectic) of the oxygen dissociation curve can be changed to the

cardiac patients as shown by numerous authors (bibliography, see Altschule), the diminution is not regular. A more pronounced arterial under-saturation indicates respiratory insufficiency, due to the diminution of lung surface, impairment of mixing or obstruction (an additional factor may be the shift of the oxygen dissociation curve). In pulmonary diseases Eppinger, Kisch and Schwarz (73) frequently observed arterial hypoxemia at rest and after exercise, in cardiac patients only exceptionally. Oxygen saturation of arterial blood may be undiminished in cases with very severe dyspnea on exertion. Harris and Lipkin obtained the same results: arterial oxygen saturation was the same before and after exercise in normal subjects as well as in cardiac patients. Himwich et al., (132) observed in one diabetic patient after moderate exercise a decrease and in another an increase of arterial oxygen saturation. In three patients with anemia oxygen saturation decreased after exercise. In one patient with emphysema (resting value 95 per cent) there was no change after exercise, and in another with the same high resting value a decrease, while in a third patient with a resting value of only 78 per cent there was a pronounced decrease during exercise. In a patient with pulmonary tuberculosis exercise produced a considerable decrease. A similar decrease of arterial oxygen saturation after exercise was observed by Harrop in a patient with anemia and by Harrop, Heath and Schaub in three patients with polycythemia vera. It is possible that the decrease is comparable in mechanism to that produced by exhaustive exercise in normal subjects. Himwich (132) suggests that the pulmonary mechanism may be the limiting factor to exercise in different diseases. As discussed in Chapter I only a very pronounced reduction of pulmonary function reduces the maximum oxygen intake. In patients with asthma and emphysema the impairment of working capacity was not dependent on either oxygen deficit or CO_2 excess in the blood, but only on the subjective sensation of dyspnea (Storm van Leeuwen and Larsen). According to Knipping (157), the determination of arterial oxygen saturation is not a satisfactory method to reveal respiratory insufficiency: the measurement of the difference of oxygen intake during exercise when breathing atmospheric air or oxygen-rich air mixtures is superior (see Chapter I).

F Oxygen Dissociation Curve of the Blood

In normal subjects the oxygen dissociation curve shifts to the right during exercise. This shift favors the diffusion of oxygen from the hemoglobin into the tissues, a greater amount of oxygen is liberated at the same oxygen tension. In cardiac patients the dissociation curve is shifted to the right at rest, and the shift becomes more pronounced during exercise. Similar findings have been obtained by Lewis, Ryffel, Wolf, Cotton and Barcroft, Eppinger, Kisch and Schwarz (74), Fider, Knipping (156), Zaeper (283), Meakins, Dautrebande et al. found the oxygen hemoglobin dissociation curves normal, but they used a very mild exercise. The shift of the oxygen dissociation curve is due, at least in large part, to the increased blood lactic acid in cardiac patients. The shift of the oxygen dissociation curve to the right is an important compensatory

CONCLUSION

The material reviewed shows that there is a quantitative rather than a qualitative difference of physiological processes in exercise in disease. The limit to which they can be increased is depressed, and this limit is reached more rapidly in disease. This is due to the fact that many mechanisms involved in muscular exercise become compensatory during rest in pathological conditions. Therefore these mechanisms are no longer available to their full extent to meet the demands of exercise, consequently working capacity is reduced or, what is the same by definition, fatigability is increased. Naturally, the impairment of various functions as well as the involvement of compensatory mechanisms vary in different diseases. The patient, naturally, realizes his diminished working capacity as subjective fatigue. This review attempts to show that fatigue and disease are intimately related. This relationship explains why fatigue is the most common complaint in disease.

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right (mesectic) by administration of thyroid preparations. Therefore, Zondek believes that the shift of the oxygen dissociation curve is the essential and primary function of the thyroid hormone.

G The Respiratory Quotient

The respiratory quotient (R Q) is about 1.0 in the beginning of muscular exercise (Hill, Simonson (243)) indicating exclusive carbohydrate combustion. From this value it drops during exercise, parallel to fatigue and the exhaustion of carbohydrate reserves (Zuntz, Durig, Furusawa, Simonson). After previous fat diet, fatigue and drop of the R Q are much more pronounced than after previous carbohydrate diet (Furusawa, Christensen, Krogh and Lindhard).

In diabetes the R Q is lower than normal in the resting condition. Inability to use carbohydrates, however, is much more pronounced during exercise. Patients with moderate diabetes are able to increase carbohydrate combustion during exercise, but the excess metabolism is much more due to fat than to carbohydrate combustion (Grafe and Salomon). According to Richardson and Levine, the failure to increase the R Q (i.e. the proportion of carbohydrates used) during exercise reflects the seriousness of the disease. In Hetzel and Long's experiments the R Q of three diabetic patients (who were obviously still in good condition as judged by their considerable athletic performances) was 0.99 in exercise of short duration after administration of insulin, while it was 0.80 without insulin. But even after insulin the R Q dropped much earlier during the exercise. The patients with diabetes behaved similarly to normals after a fat diet, but the drop of the R Q was more pronounced in the patients. Alberts and Dietrich found that the R Q = 0.95 in normal subjects in moderately heavy work with the bicycle ergometer (6,000 m-kilos within ten minutes), it was 0.91 in the average of ten diabetics without acidosis. The eleven patients in Simonson and Gollwitzer-Meier's (249) experiments were more advanced than those used by Hetzel and Long. The experiments were performed after insulin. During the short exercise of one minute duration the excess-R Q was 1.0 in 80 per cent of 46 normal subjects and in only half of the diabetic patients. This corroborates Hetzel and Long's findings that some diabetic patients are able to use carbohydrates after insulin in normal proportion. But half of the group were not able to do so, even after insulin, and the diminution of the excess-R Q was quite considerable. As low values (the lowest was 0.64) were observed after this very short exercise as in normal subjects after exhaustive exercises performed for many hours. It may be mentioned that Canzanelli and Kozadov found the same low R Q during rest and exercise (average = 0.71) in depancreatized dogs.

Simonson and Gollwitzer-Meier (250) found in two of eight convalescents from influenza an excess-R Q of 0.65 and 0.61, indicating a very low level of carbohydrate reserves. There are some indications of a reduction of carbohydrate reserves in heart disease in the experiments of Alt, Walker and Smith. A decrease of the carbohydrate reserves in cardiac patients could easily be explained by the increased lactic acid formation and excretion.

CONCLUSION

The material reviewed shows that there is a quantitative rather than a qualitative difference of physiological processes in exercise in disease. The limit to which they can be increased is depressed and this limit is reached more rapidly in disease. This is due to the fact that many mechanisms involved in muscular exercise become compensatory during rest in pathological conditions. Therefore these mechanisms are no longer available to their full extent to meet the demands of exercise consequently working capacity is reduced or, what is the same by definition fatigability is increased. Naturally the impairment of various functions as well as the involvement of compensatory mechanisms vary in different diseases. The patient naturally realizes his diminished working capacity as subjective fatigue. This review attempts to show that fatigue and disease are intimately related. This relationship explains why fatigue is the most common complaint in disease.

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MONOCYTIC LEUKEMIA

(GENERAL REVIEW OF THE SUBJECT)

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HISTORY

The general group of diseases which we know now as the leukemias has long been recognized and was described as early as the Greek age of medicine. However, for a great many years following this description, no distinction between the separate members of the group was possible, all cases were considered to be alike and were classed in what we now recognize as the lymphatic type. In 1891 Paul Ehrlich gave to the profession the aniline dyes and since then it has been possible to appreciate morphological differences within the white cell group.

In 1900 Naegeli and others were able to demonstrate that the myelocytic series was entirely different from the lymphocytic strain of cells and pointed out that myelocytic and lymphocytic leukemia were separable on morphologic grounds. During the past forty years the life histories of the lymphocyte and of the granular leucocyte have been worked out from birth to maturity and death. Their functions have been studied, their staining qualities in both fixed and supravital techniques and their behavior in tissue culture have become so familiar that the profession no longer doubts their individuality. Acute subacute, chronic and subleukemic types of each of these two divisions of leukemia are conceded by all hematologists to exist.

In 1912 with certain new techniques, Schilling (201) was able to demonstrate to his own satisfaction a third type of white blood cell which he named the "monocyte." It was therefore fitting that he and Reschad (186) should, in 1913, describe a case in which they believed "monocytic leukemia" was present. While certain other observers had described cases which, in retrospect, seem to satisfy the requirements for inclusion within this group, they were the first to state that a third type of leukemia exists and to report a case exemplifying this concept. (Both Dameshek (38) and Clough (31) call attention to a case reported by Hindenburgh (97) in 1895 which probably falls in this category. A case considered by Clough to be "highly suggestive" of the disease was noted by Rowley (195) in 1908. Other cases reported by Friedreich (73) in 1857, Ebstein (49) in 1889, Frankel (71) in 1895, and Gilbert and Emile-Weil (80) in 1899 and 1904 have been reviewed by the present author and seem to satisfy many of the criteria for inclusion in this type of leukemia.) Credit for keen observation and accurate description must be rendered to those workers but the history of 'monocytic leukemia' as a disease entity clearly stems from the work of Schilling in 1912 and 1913.

Although the preponderance of hematologic opinion at present weighs heavily in favor of considering it a disease entity, there are many well-informed and thoughtful workers in the field who still maintain that it is only a syndrome and

that it is merely a transient form of one of the other types of leukemia. These men consider the monocyte a mutation form of the myelocytic or lymphocytic series and feel that it has no separate life cycle. Even within the group who accept the monocyte as a separate cell and who believe that monocytic leukemia exists, there is much argument as to the origin of the cells of the blood in general and of the monocyte in particular. This disagreement is suggested by the multitude of names under which the disease has been reported and adds greatly to the confusion which surrounds the subject. Thus Jetter (107) reported his case under the title "Acute Leukemia," Alder (3) used the term "Myelosis," and Ross (193) "Reticulosis." Boehne and Huisman (17), Bykova (22), Ewald (54), Feller and Risak (59), Foord *et al* (64), Kato (110), Krahm (116), Luzina (135), Patrassi and Crepet (174), Rivas and Ugrumow (188) all have used the term "Leukemic Reticulo-endotheliosis" in reference to this subject alone or in conjunction with other titles. Cooke (33), Gittens and Hawlesley (81), Gledhill (82), Ramsey and Tank (182), and Foot and Olcutt (65) have referred to it as "Histiocytic Leukemia." Cornil *et al* (34), reported a case of "Monoblastic Leukemia" and Mitchell (155) used the term "Malignant Monoblastoma." "Monocytoma" was used by Lewis (131).

Since 1932 the Quarterly Cumulative Index has included all these names under the heading "Monocytic Leukemia" and has thereby greatly facilitated search for cases.

Because of the marked disparity of opinion concerning certain facts in regard to monocytic leukemia the following questionnaire was sent in June 1940 to approximately fifty authors who had written or discussed monocytic leukemia. As nearly as the author could estimate, this number represents most of the workers in the field in the United States and Canada. It was not deemed advisable to send questionnaires to the war-torn countries. From the group, forty replies were obtained, two men were reported deceased, and two had moved without leaving an address, so that of forty-six who received the communication forty or nearly ninety percent answered.

The questionnaire requested the following information

- 1 Is there such a cell as the monocyte?
- 2 Does the disease entity actually exist? If not, what is the relation of the syndrome to the other leukemias?
- 3 Are there acute, subacute, subleukemic, and chronic forms of the disease?
- 4 Approximately how rare do you think it is? By what name do you wish to designate it?

All those reporting stated that they feel there is such a cell as the monocyte. In answer to the second question, "is there such an entity as monocytic leukemia," thirty-three answered in the affirmative and only two in the negative. Four who did not answer the question referred to the opinion of some other author. Four of the best known publications on the subject were contributed by C Doan (43), H Downey (45), C Forkner (66), and E Osgood (166). The point of view expressed in these publications is fairly typical of the total thirty-three. Two who answered the question "no" were N Rosenthal (264) and W

Thompson (269) of New York Twenty-nine believe there is an acute form of the disease Two do not believe there is any such disease and, therefore that there is no acute form, and the remainder did not express an opinion The existence of the subacute form is a purely arbitrary time division Most of those reporting agree that this type was seen Twenty observers believe that there is a chronic form of the disease Three do not believe that such a form exists, and three consider that it probably exists The remainder did not answer the question specifically The existence of the aleukemic form is denied by three authors and confirmed by twenty-six The remainder did not answer the question definitely

A discussion of the wide difference of opinion concerning the frequency of the disease within the leukemic population will be given later in the text

Nearly all the authors who answered the questionnaire were in favor of leaving the term monocytic leukemia as it stands today Thompson and Rosenthal regarded them all as myelocytic leukemia and Rosenthal designates them as "monocytoid myeloblastic leukemia" Miller (259) would prefer to have them called "leukemic reticulosis," and Cunningham (235) refers to the group as "large cell lymphatic leukemia"

In the discussion of the subject the present author has attempted to include only those cases which come under Downey's classification of "monocytic leukemic—Schilling type" He has attempted to name as "true cases" only those which conform to this type since he agrees with Downey and various other workers that the Naegeli type is really myeloblastic or myelocytic leukemia

In summary it is evident that the majority of hematologists in the country believe that the disease does exist, that the name used at present is satisfactory, and that acute, subacute, chronic, and aleukemic cases are seen Most of those reporting agree to at least a two percent occurrence amongst the leukemic population, and some workers find the occurrence very much larger Nothing is to be gained by attempting to "strike an average" from these widely varying percentages

Fleischmann (62) described the second authentic case in 1915 and Bingel (15) the third in 1916 Rosenthal (190) described the fourth case in 1921 (first case from the United States) and in the same year Komiya and Hayashi (113) described the fifth case (first case in Japan) Since then the disease has been reported from Australia, China, Denmark, England, France, Holland, Italy, South America, Russia, Switzerland and various other areas The author has listed 197 cases in all of which there seemed to be some evidence that the disease existed Of these 80 have been reported from the United States, 32 from Germany, 24 from France, 15 from Italy, 16 from England, 6 from Scandinavia, 4 from Poland, 3 each from South America and China, 2 each from Canada, Russia, and Japan, and 1 each from Australia, Holland, Portugal, and Switzerland

Since the original description in 1913 excellent reviews of the subject have appeared in this country and elsewhere Dameshek (38) found 16 cases in the literature up to 1930 and added 2 more for a total of 18 In 1932 Clough (30) was able to find only 22 proven cases and added 1 more of his own to make a

total of 23 In 1934 Forkner (66) reviewed 8 additional cases from the literature and added 6 of his own to bring the total of adequately described cases to 37 In this same year Doan and Wiseman brought forward evidence which they considered sufficient to prove that cases of chronic monocytic leukemia existed and described 4 among a total of 12 personally studied cases This investigation opened the door to the inclusion of a considerable group of cases which had been previously disputed on the basis that monocytic leukemia was seen only as an acute disease In the same year Marchal and others in France and Levine contributed excellent general reviews of the subject While studying their eight cases in 1934 and 1935, Klumpp and Evans (112) were able to accept 80 cases of those reported in the literature In 1937 Osgood (166) found one hundred and twenty-seven case-reports in the literature which he was willing to confirm, and he added six more cases of his own, bringing the grand total to one hundred and thirty-three In 1938 Roversi and Salani (194) published a scholarly review of the entire subject

The author has reviewed over three hundred publications which have appeared in the literature in the past twenty-seven years and has tabulated the data from one hundred and ninety-seven cases which seemed to him to present sufficient evidence of the disease to be worthy of consideration He has further considered certain of these as being "probable" or "doubtful" cases Thus the total number of these cases which he is willing to accept without qualification is one hundred and seventy-nine

There are certain instances in which he has included cases not accepted by the previous reviewers, and other cases accepted by one or the other of his predecessors which he fails to accept This discrepancy is inevitable where the decision has to be made by different reviewers from the written page alone, and certainly nothing more than personal opinion is reflected by these inclusions and omissions

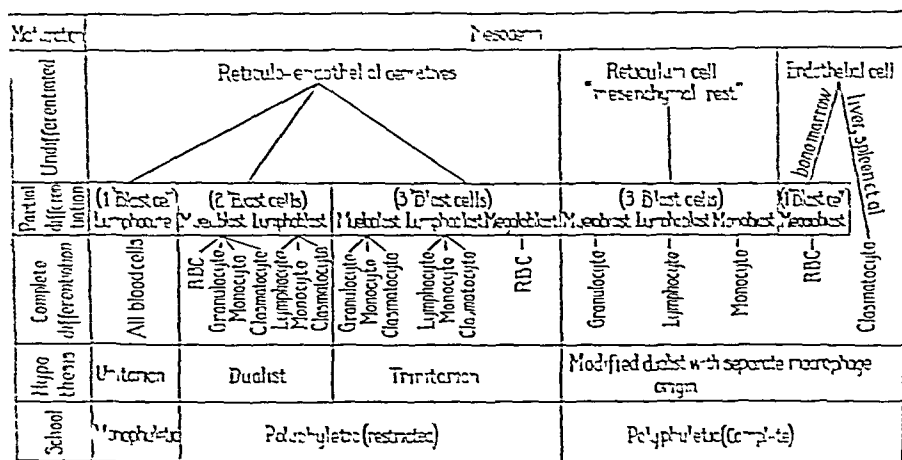
ORIGIN OF THE WHITE BLOOD CELLS

Ehrlich considered the monocyte a transition form in the course of maturation of the neutrophilic leucocyte Naegeli (162) concurred in this view as have many others Alder (3), Turk, Rohr, Brustlein (21), Hirschfeld (98), and Piney (177), Merklen and Wolfe (148, 149), Reich (184), Rosenthal (166, 264), and Thompson (269) have all felt that the monocyte has no individual origin separate from the granular series and that there is no entity which can be called "monocytic leukemia"

Amongst others, Maximow (145), Wiedenreich, Cunningham (235), and Bloom (16) have advanced the hypothesis that this cell is derived from the lymphocytic series Their reasons for this point of view are based mainly on the common morphological characteristics of the two cells

Pappenheim (173) and Ferrata clearly demonstrated the independence of the monocyte from the granular cells It remained for Schilling-Torgau to demonstrate its independence from the lymphocytic strain It is true that the monocyte is found in the bone marrow under pathological conditions only, and that it is

found in the spleen and lymph nodes normally. It is also true that tissue cultures of the monocyte and the lymphocyte are very similar. But, as Schilling pointed out in 1912, there are sufficiently great differences between the two to make it possible to differentiate them and it was with this idea and new equipment that he was the first to recognize the disease as a separate entity in 1913. Although the proponents of the lymphocytic origin of the disease are now very few, those who adhere to the myelocytic genesis of the cell are still considerable in number and great in authority. However, most hematologists now agree that the monocyte has an individual origin and that monocytic leukemia is an entity separate from the other leukemias. The relation of the monocyte to the reticulo-endothelial system and the important part played by supra-vital technique in establishing this relationship together with certain corollaries derived therefrom



REPRODUCED AFTER WISEMAN

CHART 1 SHOWS THE FOUR LEADING CONCEPTIONS OF THE ORIGIN OF THE BLOOD CELLS
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is discussed later. Final evidence that the disease is a definite entity was furnished by Doan and Wiseman when they established positively what had been suspected for some time, i.e. that there is a chronic form of the disease, and so rounded out the picture to conform with the pattern of the other leukemias.

These leading concepts of the origin of the different cells have given rise to several schools of thought on this subject, and Forkner has listed no less than nineteen separate schemas to explain their genesis. Of these only a few will be discussed here.

1. The unitarian view which assumes that all blood cells rise from one blast cell—the lymphoblast. The hematologists who still adhere to this concept are few.

2. The dualistic view in which all cells of the blood are supposed to originate from the lymphoblast and the myeloblast.

3 The trinitarian view which asserts that all blood cells stem from the myeloblast, the lymphoblast, and the megakaryoblast

4 The modified dualistic view with separate macrophage origin in which three blast cells are postulated for three white cells (myeloblasts, lymphoblasts, and monoblasts), one for the red blood cells (megakaryoblast) together with a separate origin for the clasmatoocytes

These concepts are graphically represented by Doan and Wiseman and their chart is reproduced as chart 1 with their kind permission. A further elaboration of the origin of cells is pictured in chart 2

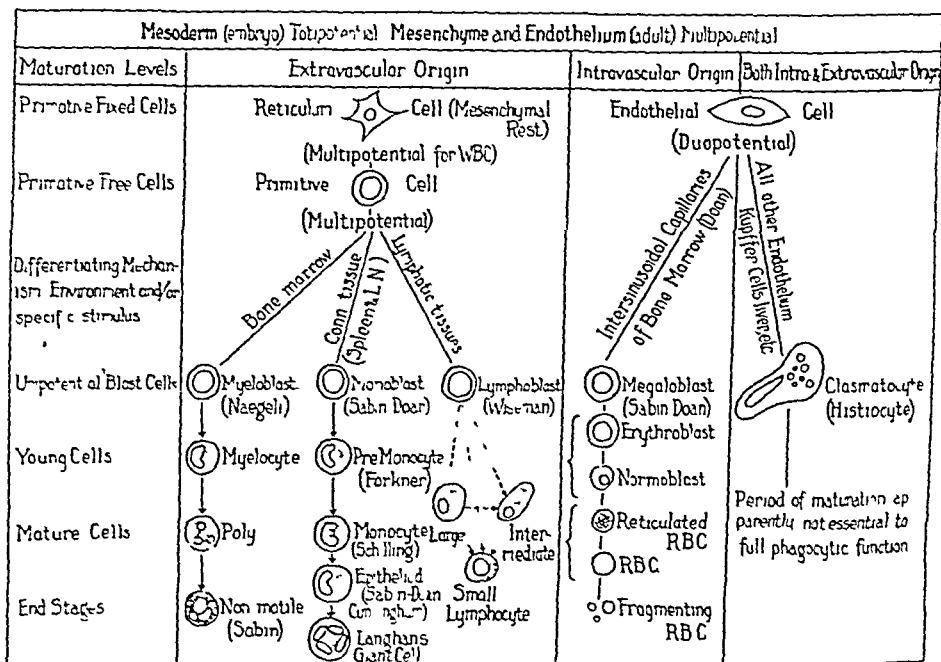


CHART 2 GIVES A FURTHER ELABORATION OF THE ORIGIN OF THE BLOOD CELLS

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The author will use the terminology and conceptions suggested by these charts in his discussion of the subject

THE RELATION OF THE MONOCYTE TO THE RETICULO-ENDOTHELIAL SYSTEM

In 1913 Aschoff and Kiyono (7) described the "reticulo-endothelial system" as being made up of highly phagocytic cells having a wide distribution throughout the body but being concentrated in number and physiologically more active in the blood-forming organs. They considered these cells to have a common mesenchymal origin and to be able to change rapidly from a sessile to an amoeboid state and back again. They included in their general schema the macrophages of Metchnikoff, the stellate cells of von Kupffer, the adventitial cells of

Marchand, the clasmatocytes of Ranvier (183), and the histiocytes of Aschoff and Kiyono. Some of these cells are so large that it would seem to be a mechanical impossibility for them to circulate in the blood as they could not pass the lung and other capillaries. The question then arose as to whether the monocyte is closely related to these tissue cells. About this same time Pappenheim (173) and Ferrata demonstrated the independence of the monocyte and the myelocyte, and Schilling-Torgau clearly distinguished morphologically between the monocyte and the lymphocyte thus establishing to his satisfaction the independence of the cell strain. When supra-vital staining was developed it was possible to show that the monocyte of the blood is closely related to, but probably not identical

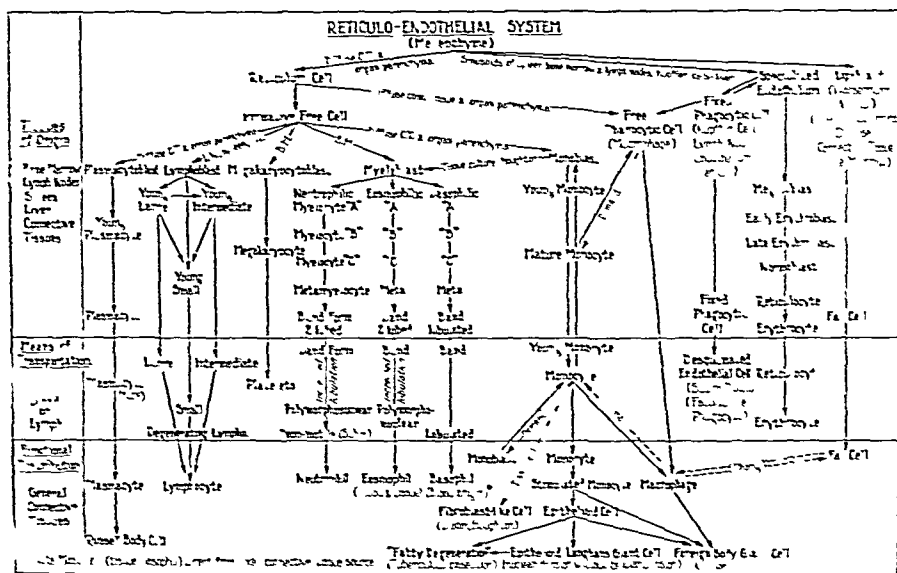


CHART 3 SHOWS THE RELATION OF THE VARIOUS BLOOD CELLS TO THE RETICULO-ENDOTHELIAL SYSTEM

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with the tissue cells. The rosette of the monocyte is found by this technique to be present in the stimulated cells and in the epithelioid cells of experimental tuberculous lesions. In fact it is assumed by some investigators that the monocyte and the tissue histocyte are merely different stages in the life cycle of the same cell.

However, the monocyte has an extra-vascular maturation cycle, is seen in the peripheral blood, has characteristic cytoplasm and nucleus and stains positively with peroxidase. The phagocytosed material is contained only in the vacuoles comprising the rosette. In the macrophage of the tissues no phenomena of maturation have been observed, the cells are extra-vascular in distribution and the peroxidase stain is negative. The phagocytosed material is distributed within the cytoplasm in large vacuoles of varying size.

The reticulo-endothelial system also bears a close relation to certain diseases in which fat metabolism is known to be disturbed. It was knowledge of this fact together with known predilection of monocytes to store lipids in certain states of disordered fat metabolism that led Doan to study the relation between fat metabolism and monocytic leukemia.

ETIOLOGY

Age

Age seems to be of little importance since cases have been recorded in individuals under one year, as those of Gittens and Hawkesley and of Jullhard, and as late in life as eighty-one years, as that described by MacKeith and Bailey. Twenty cases were reported in persons from one to nine years, seventeen in the age group ten to nineteen, twenty between the ages of nineteen to twenty-nine, forty between twenty-nine to thirty-nine, twenty-four in the age group from thirty-nine to forty-nine, twenty-three between the ages from forty-nine to fifty-nine, twenty-three from fifty-nine to sixty-nine, and thirteen in persons over seventy years of age.

Although there have been recorded about twice as many cases in men (127) as in women (61), it must be remembered that at one time the disease was considered to occur only in men. Thus some cases in women were probably overlooked in the early years.

Heredity

Heredity has not been proven to be of any importance in this syndrome and Forkner feels that the occasional cases referred to as congenital are really some other disease—possibly erythroblastosis.

Distribution

There seem to be no particular geographical limits for the disease since it has already been reported from so many widely separated areas. Judging from the past history of the disease, it may be supposed that more and more regions will be represented as knowledge concerning it becomes more widely disseminated in the medical profession. Reports of its presence in communities seem to depend in part upon the interest and equipment of the local hematological laboratories. Thus in some parts of this country it is considered a rare disease, one percent, while in others it is found as constituting approximately sixteen percent of the total leukemic incidence.

Patients of different nationalities have succumbed to the disease and it has been observed in white, yellow, and black races.

It is seen in rich and poor, in professional men and in laborers, and in country and city dwellers.

Frequency

From what has already been stated, it seems likely that the disease is considerably more frequent in occurrence than is commonly supposed and that it is

often unrecognized particularly in the more chronic form as noted by Doan (237), Gordon (248), Garon (247), Isaacs (251 104) Klumpp and Evans (112), Osgood (166 262) and others

The estimated frequency of the disease in relation to the other forms of leukemia varies all the way from Gordon's (248) estimate of 18-20 per cent of the leukemic population to Rosenthal and Harris (192) 2 per cent Doan (237), and Wiseman (271) have noted its occurrence over a ten year period as 16 per cent, Osgood (262) suggests 3-9 per cent as the general figures Isaacs (104), in 1936 very shrewdly called attention to some of the fallacies involved in attempting to figure out any general percentage but felt that the condition will probably be more frequently reported as knowledge concerning it becomes more general Some of the reasons for these wide limits are

1 The difficulty in identifying the young cells of the different strains Doan, Dameshek and many others have called attention to this factor and it is a common experience of most hematologists that those cases which are seen in the acute stage—particularly if most of the cells are very young—are extremely difficult to classify One observer will consider the blasts as myeloblasts whereas another may call them monoblasts In those geographical areas where interest in monocytic leukemia runs particularly high, the tendency will be to call them monoblasts Supra-vital staining will tend to increase the number which are called monoblasts

2 Sad experience has taught the present author that the picture seen in the blood will vary greatly from week to week or even from day to day Thus 'monocytic days' are occasionally seen in the course of myelocytic leukemia as noted in a case under observation at the present time and described later in some detail Myelocytic outpourings in the course of monocytic leukemia are very frequent and one rarely follows a case over a considerable time without finding some myelocytes in the peripheral blood At times myelocytes are so frequent on one or two examinations that one is led into error of making a diagnosis of myelocytic leukemia Less frequently young lymphocytes are also seen Obviously if the case is seen only at the time of the outpouring confusion in diagnosis will ensue It is therefore wise to base one's diagnosis on the study of preparations made over a period of some days and not on the results of one day's observation Dameshek (38 236) Schulz and Kruger (203), and Isaacs (104, 251) have conjectured that the outpouring of both myelocytes and young lymphocytes may be explained by the fact that the stimulus to monocytes which is present in the bone marrow reticulum overflows into the area of granulopoiesis in the one instance, setting myelocytes free into the blood, and in the other instance, in the lymph nodes, overflows to set free young lymphocytes

3 The diagnosis has to be made mainly on the study of the cells in the circulating blood as Beck, Dameshek, and Doan agree, and those laboratories where the supravital technique is a routine procedure will tend to report higher percentages of monocytic leukemia than those where the technique is never or rarely used Autopsy material and biopsy of lymph nodes are not as helpful in the diagnosis of the leukemias as in most diseases However, supra-vital staining of bone marrow will aid greatly in clarifying the diagnosis

Relation to infection

Krahn, Sternberg and others have considered that we are not dealing with a disease at all but merely with a symptom-complex and that this syndrome is an unusual reaction to infection. In support of this contention it may be said that there are several instances in which the response to micro-organisms is monocytic. Thus a monocytosis is seen at certain stages of tuberculosis and Sabin has described monocytic invasion of the early tubercle before its replacement by lymphocytic cells. Certain of the yeast infections call forth a monocytic response and some of the other infections may have a period of monocytosis. However, descriptions of prolonged monocytosis of significant proportions and more particularly of all stages in the life cycle of the monocyte are not available. In working with the bacillus *monocytogenes* in rabbits Murray, Swan, and Webb (161) were able to produce a distinct monocytosis both in the peripheral blood and in the tissues, but their work has not found its counterpart in human beings since the bacillus has not been found in connection with monocytic leukemia. Wyschegorodzewa (228) described a case of monocytic leukemia with a positive blood culture of staphylococcus and Klumpp and Evans (112) found the *Bacillus coli* in blood culture from one of their cases but in each instance the cultures were probably merely terminal as they had been preceded by negative cultures. Vincent's spirilla have been noted many times in smears from the mouth lesions seen in the disease (Klumpp and Evans (112), Lawrence, Josey and Young (125), Levine (129), Whitby and Christie (224), and others). Their presence is not diagnostic and may be due to the absence in the lesions of protecting granulocytes as in malignant neutropenia. Foord and Parsons (64) found the staphylococcus in the leukemic lesions and Klumpp and Evans (112) isolated the *Bacillus pyocaneus*. As the case reports multiply without any real evidence for bacterial origin of the disease, the hypothesis that it is due to any specific micro-organism or is an unusual reaction to several different bacteria becomes less and less tenable just as it has in respect to the other forms of leukemia, in spite of its clinical similarity to infection.

The various laboratory tests for syphilis, and the Paul-Bunnell reactions have been consistently negative.

Metabolic background

Concerning the possible metabolic background for the disease much is conjectured and recently a good deal of suggestive evidence has been submitted. Following studies of the effect of tuberculo-lipoids on monocyte-epithelioid proliferation reported by Sabin and Doan (42) and confirmed by others, Doan and Wiseman (43) suggest and present certain supporting evidence that disturbance in lipid metabolism may play a part in monocytic leukemia, particularly in the chronic cases. They call attention to the following probabilities: (1) the selective phagocytosis of fats by monocytes, (2) evidence of excess of plasma lipoids in cases of monocytic leukemia, (3) the occurrence of monocytic hyperplasia in other diseases associated with proved disturbance of fat metab-

olism (tuberculosis, Niemann-Pick's Disease, Hand-Schüller-Christian's Disease, Gaucher's Disease, and possibly Hodgkin's Disease), (4) the fatty vacuolization of the monocyte. In this connection they discuss the case reported by Marchal and Bargeton, which seemed to show a transition from Hodgkin's Disease to monocytic leukemia during a period of observation. More recently Miller has stated that there is a close relation between Hodgkin's Disease and Chronic aleukemic monocytic leukemia and Osgood feels that there is much probability that the two conditions are identical. Doan and Wiseman feel that monocytic leukemia begins as a disturbance of fat metabolism which results in monocytic proliferation. They feel that chronic cases can possibly be controlled to a certain extent by care of this disordered state. When the reaction has reached an irreversible state, a neoplastic disease ensues.

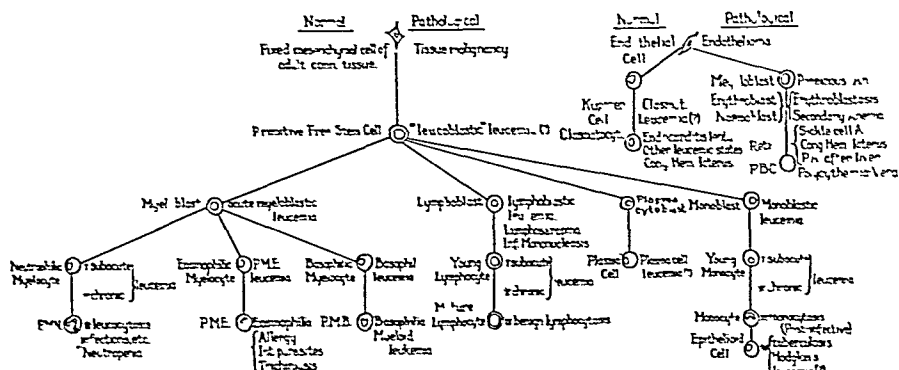


CHART 4 SHOWS THE RELATION OF CERTAIN BLOOD CELLS TO DISEASE

Reproduced by permission of Dr. Charles Doan

Relation to newgrowth

Many pathologists have maintained for a long time that the acute form of the disease is a new growth. Latterly hematologists and clinicians have leaned more toward this view. This opinion is suggested by the fact that the cells are found invading nearly all the tissues of the body in a most unbridled manner. Lesions of the bones, which appear very similar to those seen in the metastases of carcinoma, have been demonstrated. The cells themselves partake of irregular mitotic division in areas where mitosis does not normally occur. A great deal of experimental work has been done on mice with a neoplasm simulating very closely monocytic leukemia of human beings. Thus, J. Furth (76) and J. and O. Furth (75) have produced this new-growth by the injection of benzopyrene and have studied resulting neoplasms of the monocyte in mice. M. Lewis (131) reports on the transference of mouse neoplasms and on tissue cultures in this mouse disease. While this evidence is not directly conclusive, it has seemed to many hematologists that the acute form of monocytic leukemia partakes in many ways of the nature of neoplasms. Whatever else may be said

of its fundamental nature, it must be admitted that it resembles clinically the other forms of leukemia very closely

PATHOLOGY

The pathological lesions of monocytic leukemia are extremely widespread, and eventually nearly all the organs of the body may be invaded by the type cell unless death ensues before dissemination of the cells in general or unless there is some obstruction to delivery of cells to the peripheral blood such as apparently occurs in the subleukemic cases. Under these latter circumstances it may happen that the distortion of normal physiology is limited to those organs which contain a large quota of reticulo-endothelial tissues such as the bone marrow, spleen, and lymph nodes.

The spleen is nearly always enlarged though the increase in size may come only late in the disease and in other instances may be found only at post mortem examination and not be evident clinically. The liver is enlarged almost as frequently as the spleen and has seemed to this author to be a more constant finding in this type of leukemia than in the others. The lymph nodes are very often enlarged and tender though it has seemed to some writers that their enlargement is sometimes secondary to areas of adjacent infection and ulceration. The bone marrow has given evidence of change in structure in nearly every instance in which it has been submitted to study.

In the acute cases ulceration in the oral cavity, hemorrhage into the skin and digestive organs, and painful enlargement of the lymph nodes are frequently observed in addition to the findings noted above. In the chronic cases the spleen, liver, and lymph nodes are also palpable but ulceration and hemorrhage are less often noted. Skin nodules, bullae, and purpura are frequently present in this group.

Gross pathology

At post mortem examination the outstanding pathological processes observed are hemorrhage, ulceration, and hyperplasia of the reticulo-endothelial tissues.

Hemorrhage is seen in nearly all cases and has been described in the skin by many observers. Both purpura and petechiae have been reported on many occasions and the "hemorrhagic diathesis is very evident" (Schultz and Kruger (203)). Hemorrhage from some area in the oral cavity is extremely frequent and the gums seem to be more often involved than any other single structure. Bleeding from the stomach is not infrequent. The pleura, pericardium, peritoneum, meninges and kidneys have also been found to be hemorrhagic (Lawrence, Josey and Young (125)).

Leukemic thrombosis of the heart itself was described by Orr (165), and Klump and Evans (112) found thrombosis of the pulmonary artery by leukemic cells.

Anemia of all organs is the rule unless the disease is so acute that there is no time for its development. Ulceration with necrosis, pseudo-membrane formation and gangrene is very often seen and may be clinically similar to that seen

in malignant neutropenia The oral cavity is the commonest site for these lesions and the gums and buccal mucosa are particularly liable to involvement The trachea and larynx may present ulceration as observed by Schulz (202), Bock and Wiede (20), Schilling (200), Wyschegorodzewa (228), and others Ulceration is seen in the stomach and jejunum and when present in Peyer's patches is similar in appearance to that found in typhoid fever (Orr (165), Schilling (200) Hittmair (99), and others)

Hyperplasia of the reticulo-endothelial structure has been noted in the bone marrow by Osgood (166) and others, in the spleen by Schilling (186), Osgood (166), Bock and Wiede (20), Klumpp and Evans (112), and many others

Increase in size of practically any organ may be present due to infiltration by monocytes in large numbers

MICROSCOPIC PATHOLOGY

Infiltration of the skin by monocytes together with hemorrhage has been noted by a great many authors and has been described in detail by Mitchell (155), Osgood (166), Klumpp and Evans (112), Schilling (186), Sydenstrcker and Phmzy (212), and Whitby and Christie (224)

There is hemorrhage, ulceration and a notable lack of granulocytes in the lesion of the mucous membranes as has been described by Bingel (15), Hittmair (99), Orr (165), Schilling (200), and Wyschegorodzewa (228)

Proliferation of the sinus reticulum has been noted in the spleen by Bingel (15), Schilling (186), Ugrimov (217), Wyschegorodzewa (228), and others Distortion of the normal architecture with thickening of the stroma, areas of necrosis, hemorrhage and distention of the sinuses has been repeatedly found in the spleen and lymph nodes

In the liver sloughing of Glisson's Capsule and infiltration with monocytes has been described by Gittens and Hawkesley (81), Grenet (88), Klumpp and Evans (112), Levine (129), Ugrimov (217), and Wyschegorodzewa (228) Swelling and edema of Kupffer's cells has been noted by Dameshek (38), Bock and Wiede (20), Ugrimov (217), and Wyschegorodzewa (228), but Merklen and Wolf (148), Watkins and Hall (220), and others have found that they remain normal Increase in the number of reticular cells, hemorrhage and areas of necrosis have also been reported

Dameshek (38), Swartzchewaja (211), and Wyschegorodzewa (228) have called attention to the presence of myeloid islands in the bone marrow sinuses (intra-vascular origin) and Dameshek (236) and others have postulated that this fact explains the presence of young granular cells in the peripheral blood He feels that the stimulus which gives rise to the abnormal production of monocytes in the bone marrow reticulum may overflow into the granulo-poietic area and cause this condition Infiltration with monocytes and general reticulum hyperplasia are the rule and have been noted so often that reference to individual publications does not seem necessary Late in the course of the disease myelophthisic marrow is apt to be seen due to crowding out of the normal structures by monocytes

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PATHOLOGY

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technique be stained in the tissues sufficiently well to be easily differentiated. Material from bone marrow punctures lends itself particularly well to staining with various dyes.

In the fixed spread there is usually little difficulty in recognizing the adult cells of this series but when one meets the immature members of this strain greater difficulty is frequently encountered. It is in these instances that the supra-vital technique is a necessary adjunct to diagnostic methods employed in the examination of both blood and bone marrow. Although living cells of the blood were examined previous to the work of Sabin (197) and her collaborators, the leading exponents of this form of blood study and particularly of its application to clinical hematology have been recruited from her group and Doan (237) has stressed the very real practical importance of supra-vital studies. In fact every blood dyscrasia is studied routinely in his laboratory and clinic by this method and his final judgment is frequently largely based on the results of this mode of study of the blood and bone-marrow in difficult cases.

In preparations of the blood or tissues made by the fixed stain method the monocyte is seen as a large round or oval cell with round oval or indented nucleus. The cytoplasm of the cell is abundant and stains homogeneously blue-gray in a manner frequently referred to as 'ground glass'. While the much discussed azurophile granules are usually grouped about the 'hof' of the nucleus this is not always the case and they are sometimes seen in the periphery of the cytoplasm. At some time in the course of most cases of monocytic leukemia monocytes are found which show vacuolization of the cytoplasm. These vacuoles have been considered by some observers as evidence of fatty deposits in the cell. They are found more frequently in this strain of leukemic cell than in either of the other two. Clough (30) observed a tendency of the granules to group about phagocytosed inclusions. Occasionally phagocytosed red blood cells can be seen shining through the cytoplasmic covering. The nucleus is round oval indented or twisted upon itself, usually eccentric in position and surrounded by a perinuclear 'clear space'. It is large vesicular and gives the impression of marked thinness with very 'spongy' chromatin network. It stains from light red to purple in color. Nucleoli are usually present but their absence does not militate against classing the cell as a monocyte as some workers have held nor does their presence indicate that the cell must be assigned to another strain as others have held. There are rarely more than two nucleoli in any one nucleus. In the fixed smear evidence of motility of the cell is furnished by the presence of frequent cells with irregular cytoplasmic contours. These are what were described by the earlier workers as 'pseudopods'.

Monoblasts are frequently smaller than adult cells. They are round or oval and the nucleus is usually round or slightly oval. Nucleoli are usually seen. The youngest of these cells resemble very closely myeloblasts and lymphoblasts. The cell substance is made up of dense blue cytoplasm the chromatin is mottled and purple in color. Nucleoli are relatively large and roughly spherical. As the cell grows to maturity the cytoplasmic granules become smaller and stain less densely. Azurophilic granules do not appear until the promonocyte stage.

Proliferation of the reticulo-endothelial structures in the lymph nodes is very often reported and as Dameshek has pointed out may account for the presence of young lymphocytes in the circulating blood just as the similar state in the bone marrow may produce young granular cells. Necrosis and hemorrhage are very frequently seen in the lymph nodes.

Infiltration with the type cell, necrosis and hemorrhage may be seen in almost any of the organs if the course of the disease is protracted.

Because of the controversy concerning the existence of chronic forms of the disease, the pathological conditions which have been described in certain instances are discussed at some length. In general it may be said that the lesions seen in acute cases are often duplicated in those which run a subacute or chronic course, though ulceration and necrosis of the mucous membrane is less common. Hemorrhage is frequent and proliferation of the reticulo-endothelial system is the rule. Most of the organs are infiltrated by monocytes just as in the more acute cases. Enlargement of the spleen, liver, and lymph nodes has been very often reported. Thus in cases which have survived for thirty or more weeks hemorrhage into the skin has been found by Komiya (113), Swirszczewaja (211), Böhne and Huismans (17), Sydenstricker (212), Dubinskaja and Batalchuk (46), Orr (165), Osgood (166), Foot and Olcott (65), Forkner (22), Griffin and Watkins (79), Mitchell (155), Whitby and Christie (224), Klumpp and Evans (112), Roversi and Salanis (194), and others. Ulceration of the skin and mucous membranes has likewise been found by many observers. Doan and Wiseman (43), Dubinskaja and Bakalchuk (47), Farley (57), Foot and Olcott (65), Forkner (66), Klumpp and Evans (112), Komiya and Hayashi (113), Mitchell (155), Orr (165), Osgood (166), Powell (181), Roversi and Salanis (194), Schwirszczewskaja (211), Sydenstricker (212), and Whitby and Christie (224). Likewise enlargement of the spleen, liver and lymph nodes in chronic cases has been noted in Dubinskaja and Bakalchuk (47), Forkner (66), Klumpp and Evans (112), Komiya (113), Marchal and Lemoine (141), Mitchell (155), Osgood (166), Roversi and Salanis (194), Swirszczewskaja (211), Böhne and Huismans (17), Mallory (23), Powell (181), and Sydenstricker and Phinzy (212) all report enlargement of the spleen and liver.

Perhaps the most characteristic finding in the lesions of the chronic cases is a histological picture very similar to or identical with Hodgkin's Disease. Eosinophilia is marked and Dorothy-Reed-Sternberg cells are also seen. Marchal and Bargeton (139) called attention to this similarity and it has since been noted by Doan (43), Miller (154), and Osgood (166).

Thus it would seem that the pathological features of the disease which are present in the acute cases are all seen also in those which run a subacute or chronic course.

MORPHOLOGY

The monocyte is a large cell, its diameter varying from fifteen to thirty micra. It is normally larger than the polymorphonuclear granular cell. While it is easier to stain in the blood spread than in the tissue, it can, with the proper

technique be stained in the tissues sufficiently well to be easily differentiated. Material from bone marrow punctures lends itself particularly well to staining with various dyes.

In the fixed spread there is usually little difficulty in recognizing the adult cells of this series but when one meets the immature members of this strain greater difficulty is frequently encountered. It is in these instances that the supra-vital technique is a necessary adjunct to diagnostic methods employed in the examination of both blood and bone marrow. Although living cells of the blood were examined previous to the work of Sabin (197) and her collaborators, the leading exponents of this form of blood study and particularly of its application to clinical hematology have been recruited from her group and Doan (237) has stressed the very real practical importance of supra-vital studies. In fact every blood dyscrasia is studied routinely in his laboratory and clinic by this method and his final judgment is frequently largely based on the results of this mode of study of the blood and bone-marrow in difficult cases.

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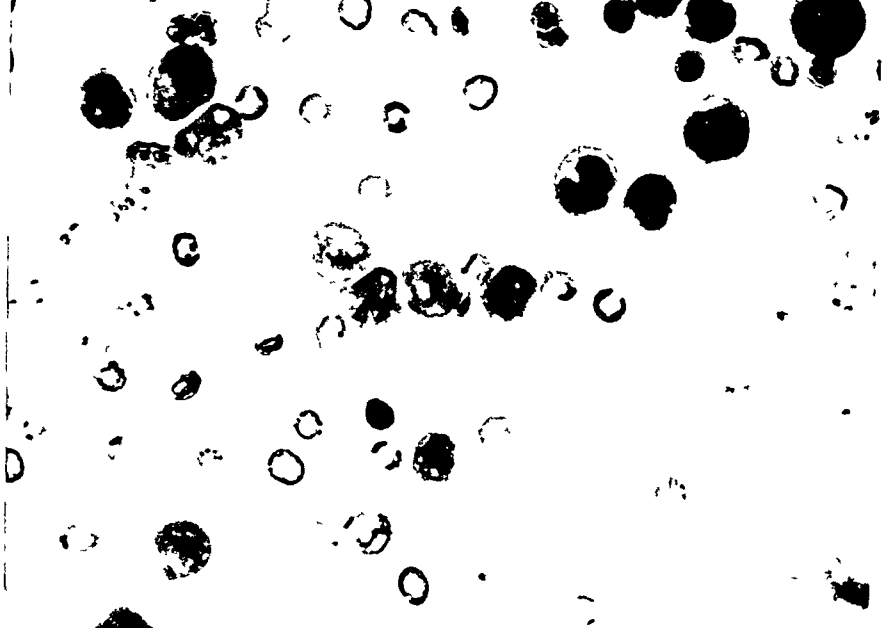


PLATE 1

BLOOD SPREAD OF CASE 1 (KLUMPP AND EVANS) $\times 500$

The cytoplasm is abundant and homogeneous. The nucleus is large and of many different shapes from roughly round to actually kidney-shaped or lobulated. Nucleoli are seen. The irregular cytoplasmic outlines are evident. The dark areas in the red blood cells are artefacts.

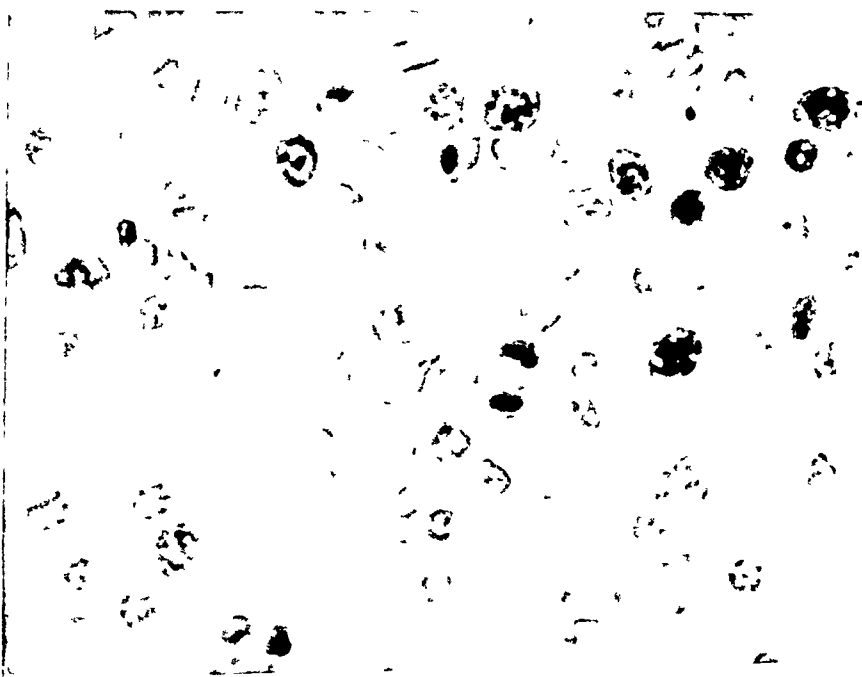


PLATE 2

STERNAL MARROW (KLUMPP AND EVANS CASE 4)

The type cells are frequent. A dividing monocyte is seen near the center of the photograph.

is reached but some vacuolization may be seen in the later monoblasts. Graphic representation of the changes occurring in maturation is reproduced by permission of Doan.

In supra-vital studies under the direction of a hematologist thoroughly familiar with the technique the monocyte can be easily distinguished and the monoblast can usually be identified. Characteristics of this cell are (1) surface film motility (2) grouping of the vacuoles stained with neutral red in a rosette usually in the hof of the nucleus (3) scattered fine mitochondria stained with Janus green. Actual motility is seen only when prolonged study is made and is demonstrated best by moving picture films. Supra-vital studies can be made in the laboratory but preparations of the material must be made immediately upon

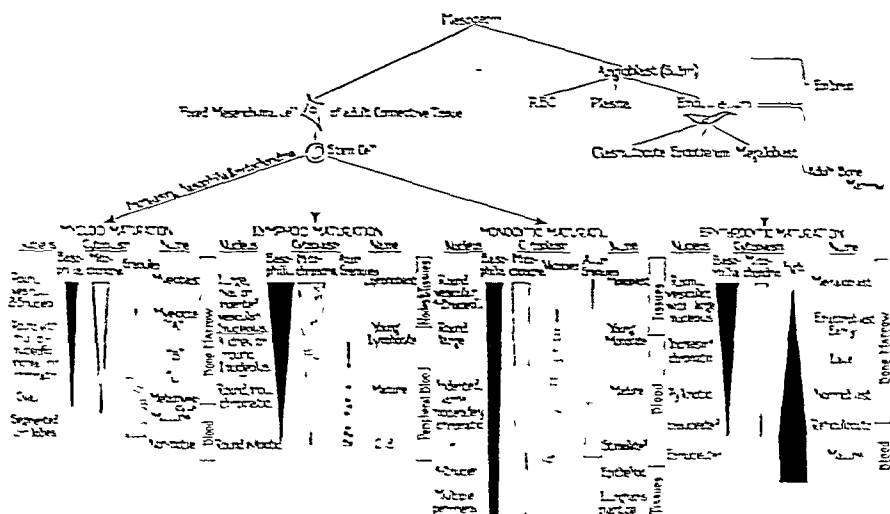


CHART 5 SHOWS GRAPHICALLY THE STRUCTURAL CHANGES WHICH OCCUR IN THE VARIOUS BLOOD CELLS DURING MATURATION.

Reproduced by permission of Dr. Charles Doan.

withdrawal of the blood or bone marrow. If kept in the icebox at optimum temperature the cells remain alive for some hours, occasionally as long as twenty-four hours, but after being placed upon the microscope stage their life does not usually exceed one-half to one hour.

Although the value of the peroxidase stain has been found to be less than that of the supra-vital technique, it is of sufficient importance to be used in selected blood dyscrasias. Monocytes usually stain positively but not as deeply as myelocytes and the number of granules is less. For more detailed description of these cells the reader is referred to a recent publication of Beck (14).

HEMATOLOGY

In any discussion of the blood it must be remembered that what one actually sees in the peripheral blood is a parade of cells from their source of origin to

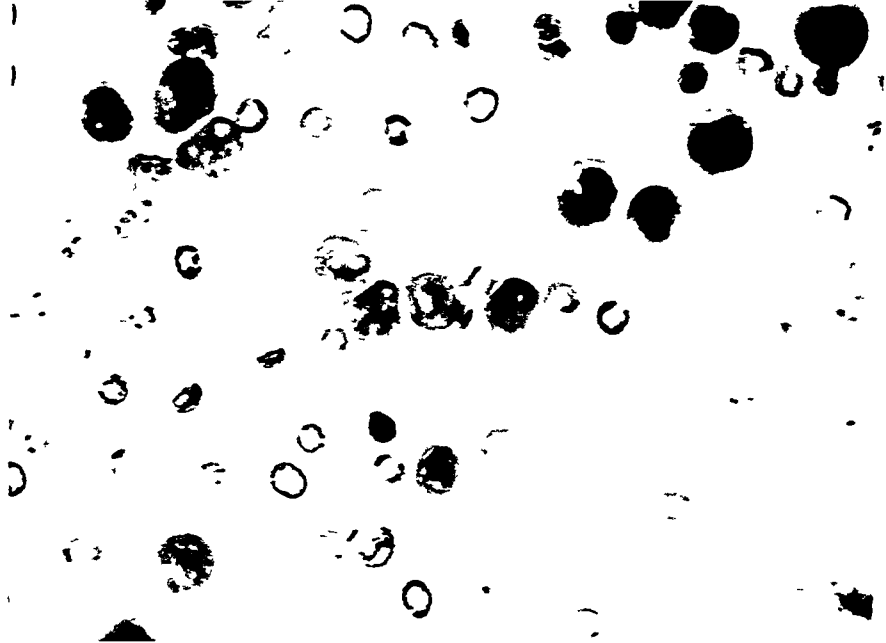


PLATE 1

BLOOD SMEAR OF CASE 1 KLEMPERER AND EVANS, X 500

The cytoplasm is abundant and homogeneous. The nucleus is large and of many different shapes from roughly round to actually kidney-shaped or lobulated. Nucleoli are seen. The irregular cytoplasmic outlines are evident. The dark areas in the red blood cells are artefacts.

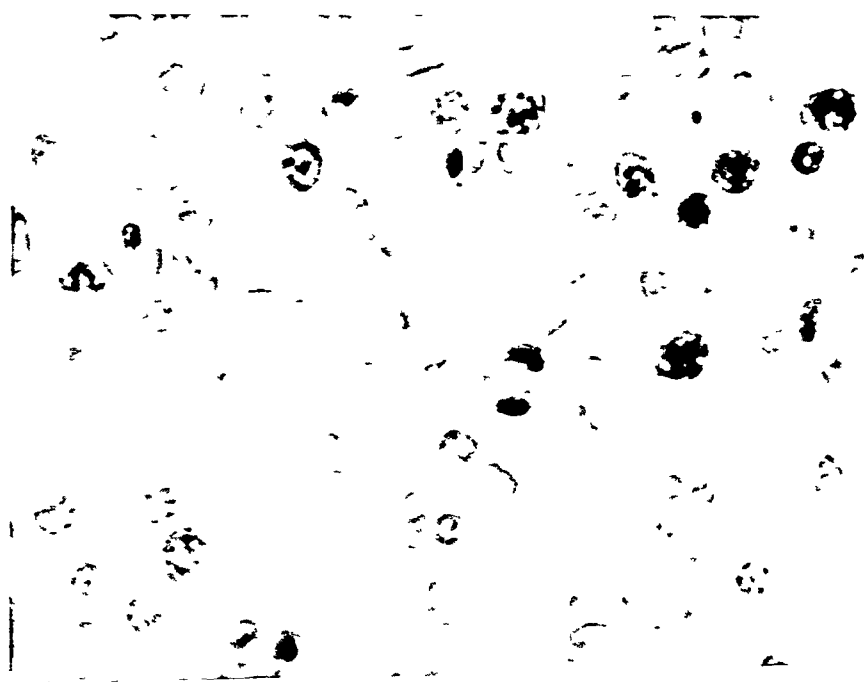


PLATE 2

STERNAL MARROW KLEMPERER AND EVANS, CASE 1

The type cells are frequent. A dividing form is seen near the bottom of the photograph.

of immature cells from day to day and this is actually the case. Sometimes showers of this type of cell appear and then disappear suddenly. Some reports have been made of individuals in whom the vast majority of cells were promonocytes or monoblasts (Farrar and Cameron (58) 86%, Levine (129) 76%, Lynch (136) 90%, Eversen (53) and others 80%) at one or more examinations. Some caution should be used in interpreting these figures since not all observers are in agreement as to what constitute the criteria for identification of the monoblast.

As for the average monocyte count of the acute case it seems fair to say that the counts vary so widely in any individual from day to day and from individual to individual that it is useless to take any figure as average. They may vary all the way from a few thousand to four hundred thousand per cubic millimeter. The same holds true in the subacute and chronic cases.

MONOCYTIC LEUCEMIA

	Erythrocytes	Leucocytes	Platelets	Megakaryocytes
Peripheral Blood	Secondary Anemia	Monocytosis	Thrombocytopenia 22,000 to 90,000	None
Bone Marrow	Hypoplasia	Monocytic Infiltration	—	Absent to occasional
Clinical Evidence of hemorrhage	Purpura, bleeding gums, retinal hemorrhage, epistaxis			

CHAPTER 6 SHOWS THE BLOOD AND BONE MARROW FINDINGS IN RELATION TO THE CLINICAL OBSERVATIONS

Counts of the lymphocytes vary directly with the damage done to the lymphogenic tissue. Until the damage is severe changes may not be great though the normal lymphocytic-monocytic ratio is reversed very early. Young lymphocytes and lymphoblasts are sometimes observed and Dameshek feels these are due to stimulation of lymphoid tissue by adjacent reticular overgrowth.

From what has already been said it would seem obvious that the granulocyte counts are not much changed early in the disease since the granulopoietic portion of bone marrow is usually spared for some time but the appearance of a few myelocytes is almost universal in those cases where they are sought for carefully and occasionally they are present in rather large proportion (Le Blave and Char-dac (127) case 30%, Down and Wiseman (43) case 33%). Later in the course of the disease when there is invasion of the bone marrow with crowding of the myeloid tissue granulopoiesis is damaged granular cells are greatly reduced in number and veer to the left by the same mechanism described by Dameshek. Sometimes almost complete agranulocytosis occurs together with the typical clinical entity of angina (Klumpp and Evans (112)).

their destination in the tissues" (Doan (237)) With this concept in mind it is far easier to understand the extreme variation in numbers of cells and their morphological characteristics which is so often observed in leukemia. In no other form of leukemia is this more true than in the monocytic type. In this disease the blood reflects directly what is going on in the spleen, lymph nodes, bone marrow, and other organs having reticulo-endothelial structure.

The monocytes of the circulating blood are identical with those seen in the spleen and lymph nodes. As has already been stated, these are the areas where production and maturation normally take place and it is in these areas that the first evidence of change in number and structure of cells occurs when leukemia develops. Presumably these changes begin some time before delivery of cells to the circulation is effected and some cases of reticulo-endotheliosis without large numbers of circulating monocytes but with typical pathological findings in the tissue (subleukemic variety) have been reported. One reason for this assumption is that in those instances where peripheral blood is relatively normal, lymph nodes removed for biopsy are found to be typical of the disease. Of course these cases are usually of the chronic type. Another reason for this assumption lies in the fact that some individuals may show slight qualitative changes in the blood picture for some time and then the blood suddenly becomes markedly leukemic in character both qualitatively and quantitatively. One may liken the condition in the spleen and lymph nodes to that of a stream where a dam is suddenly established. Water is present in the reservoir for some time before it appears below the area of obstruction.

In an acute case of the disease monocytes multiply in the spleen and lymph nodes rapidly. In the vast majority of acute cases they are delivered to the circulating blood in large numbers and are thus transported to other tissues which they invade. Usually a good many young monocytes, or promonocytes, are also present in the peripheral blood and in most instances where the blood is examined on numerous occasions monoblasts are found at some examination. It is probable that in most reported cases where the monocytes are described as almost entirely of the mature type, there were occasions when younger cells might have been found had examination been made.

Occasionally descriptions of the disease have appeared in which the blood was aleukemic but in which the course was short. In these instances delivery of cells to the circulating blood might be assumed to be impeded and one would expect to find the usual tissue evidence of the disease. This is exemplified by the reports of certain cases by Bykova (22), Grenet (88), and others, Marchal (140), and others, Levine (129), Penati and Levi (176), Kato (110), Osgood (166), and by others.

Since the delivery of the cells and their transportation to the tissues is undoubtedly somewhat irregular, one would expect great variations in the number of cells in the circulating blood on different examinations and this is what one finds. Counts may vary as much as 320,000 in a few days (Klumpp and Evans (112)), and increases or decreases of several thousand may be recorded on ensuing days. By the same token one would expect great variation in the number

acute case duration is measured in days or weeks in the subacute case in months and in the chronic case in years

Like other forms of leukemia cases of aleukemic type or with aleukemic intervals do occur though the most common form is the leukemic type. In this respect it should be remembered that it is far easier to make the diagnosis in those cases where monocytes are in abundance in the peripheral blood than in those where the peripheral monocyte count is low in spite of the fact that the tissues supply incontrovertible evidence of the disease. Undoubtedly many such cases are never brought to the attention of the hematologist and are considered to be merely unusual reactions to infections or are never diagnosed at all. Such cases have been reported by Bykowska (22) Gregg (87) Levine (129) Penati (176) Kato (110) Osgood (166) and others.

Cases beginning as leukemic types with high peripheral white cell counts and ending with or at least having intervals of leucopenia have been reported by Marchal (140) Klumpp and Evans (112) Tullhard (108) and others. So far cases starting out as polycythemia and ending as typical cases of monocytic leukemia have not been described though it is reasonable to expect that such cases do occur and will eventually find their way into the literature.

Combination of this disease with various neoplasms has been noted by Gittens and Hawkesley (81) Mesrupyan (151) Gump (89) and by others.

Skin lesions have been noted by many observers and several of the cases have been reported almost exclusively from that standpoint as those of Montgomery and Watkins (156, 157, 158) Lynch (136) Mercer (147) and others. These lesions are varied in nature. Petechiae are so common as to be almost the rule. Purpuric lesions have frequently been noted. Nodules which may either disappear or break down into ulcers seem to have been the lesions of major interest to the dermatologists. Bullae have also been described in these cases. One or several of these skin lesions is usually present at some stage of the illness and disturbances of the sort are far more common than in the other types of leukemia.

Ulceration of the gums and bleeding from them have been reported in a vast majority of cases—very frequently as the first symptom—and therefore it is not uncommon to find that the patient visits a dentist for the removal of a tooth or teeth before he consults the physician. Bleeding is often found to be intractable and the individual consults an internist for that reason. Lesions of the throat are not as common as those of the gums but angina and ulceration have been reported very often.

The spleen is usually found to be somewhat enlarged and might be said typically to be intermediate in size between that of lymphatic and that of myelogenous leukemia. Cases have been found in which the spleen was normal throughout the course of the disease (Bykowska (22) Clough (31) Orr (165) Dameshek (38) Farley (57) and many others).

The liver is frequently large and is occasionally palpable in instances where the spleen is not enlarged. It is my impression that this organ is more frequently enlarged early in this type than in the other types of leukemia.

Undoubted cases of the disease without any lymph-adenopathy are on record

What has been said of the granular cells applies almost exactly to the red cells also. The mechanism is the same and the counts are relatively normal until myelophthisic marrow develops. From that time on anemia is severe, of rapidly increasing intensity, and young red cells are often seen.

The thrombopoietic function of the marrow is frequently depressed early and low thrombocyte counts are often found in this type of leukemia.

The hemoglobin and serum iron levels parallel roughly those of the red cells and are also measures of the intensity of the bone marrow damage.

SYMPTOMS AND PHYSICAL SIGNS

It was assumed by some of the early workers that only an acute type of the disease exists but today there is little doubt of the clinical existence of subacute and chronic forms as well. This fact is very important since it allows the inclusion of numerous cases which satisfy all other requirements of the disease and since it rounds out the disease entity to conform with that of the other leukemias. Subacute cases were early described by Fleischmann (62), Komiyama and Hatahara (113), Switschewskaja (211), Wyshegorodzewa (228) and Farley (57) in all of which the duration was between thirty and forty-five weeks. Lawrence (125), and others, and Cuatrecasas (36) described cases which were known to exist for fifty-six weeks. However, it was not until Doan and Wiseman's (43) classic description in 1934 that all doubt of the existence of the less acute forms of the disease seems to have been removed. Marchal (140), and others, Osgood (166), Grenet (88), and his collaborators, Roversi and Salani (194), have all described cases which lived for over two years. Some of these cases have remained chronic throughout the entire course of the disease and others have had distinct remissions such as Fleischmann's (62) and Mallory's (23) cases. Now if this disease is subject to remissions and has long-enduring periods of relative freedom from symptoms, cases may frequently occur in which the disease has existed for a long time before diagnosis is made. In these instances it is quite reasonable to assume that some acute episode might be simply the match which lighted a fire already laid with tinder. This has led in one instance (Klumpp and Evans (112)) to legal discussion as to the average duration of the disease and average life expectancy of an individual who suffers from the condition. It must be obvious to any one who has studied the subject that no generalization can be applicable in any given patient in this respect and that each case should be judged on its own merits.

By far the majority of cases have been of short duration after the diagnosis was once made. In some instances only a few days have elapsed from the time of diagnosis to death while in others the duration has been as long as two hundred weeks. Exact figures as to the average duration do not seem to be of great value since so many factors enter into the determination. Thus the disease may exist for a long time before its discovery and since the duration is usually given on the basis of the first symptom noticed by the patient, the interpretation of the history taken by one individual is apt to differ from that taken by another. However, it might be fair to say that from the time of diagnosis to death in the

Skin lesions of long duration and of varied types are common. In this group exfoliative dermatitis, nodules, and ulcers are commonly described. Lymph nodes may or may not be enlarged, and the same holds true of the liver. The course is long, usually measured by months and rarely in years. The patient in general runs a course closely reminiscent of chronic lymphatic leukemia. Death eventually ensues from exhaustion and intercurrent infections or some circumstance unrelated to the leukemia.

Between the two extremes are the subacute cases which resemble the acute case in that they have the mouth lesions, and the chronic cases in that the symptoms are minimal for a considerable time after the diagnosis is made. The termination may be similar to that of the chronic cases, or an exacerbation may occur resulting in a picture no different from the acute type. A division into "subacute" is therefore a completely arbitrary one based on the time interval intermediate between the acute course and the chronic one.

The blood counts in both the acute and chronic cases have been described elsewhere. The aleukemic type may be either parallel with the acute or chronic, and may have the clinical feature of either one.

DIAGNOSIS

"Si sur la vaste scène de la pathologie, vous deviez choisir un problème particulièrement difficile, il est bien possible que votre choix s'arrêterait sur le caprice des leucémies" (Annes Dias (40))

Acute monocytic leukemia with high peripheral blood count and a large proportion of adult cells of this strain is not difficult to distinguish from other syndromes. The presence of proliferative lesions of the gums and throat, the thrombocytopenia, splenomegaly—between that of the other two types—the large liver, the relatively slight lymphadenopathy and the characteristic skin lesions all serve to make the diagnosis likely. It can be then confirmed by supravital blood studies and bone marrow examination. The blood in these typical cases is characteristic with many adult monocytes and a sprinkling of young cells and monoblasts. But even in these apparently "text-book" cases one should examine a series of blood spreads over a number of days or weeks if possible. Only recently Doan has studied with me a case of myelocytic leukemia for a period of twelve months. During this period it was possible for him to demonstrate a complete cycle in the disease: early in its course there was a preponderance of young myelocytes and myeloblasts, this stage was followed somewhat later by a period when the cells were beginning to tend toward maturation with many myelocytes of greater age and a few band forms and adult polymorphonuclear granulocytes. Still later the myelocytes nearly vanished from the peripheral blood. At one examination in this otherwise typical case, a shower of monocytes and monoblasts occurred so that they made up a large percentage of all the white cells in the circulating blood. Had this been the only occasion on which the blood was examined, a diagnosis of monocytic leukemia might have been made.

Recently (May, 1941) Hall and Watkins reported a case observed for a period

as those of Dameshek (38), Cooke (33), Orr (165), Doan and Wiseman (43), and many others. Sometimes there is general lymphadenopathy but very often it is limited to the cervical nodes, draining ulcerated gums, or tonsils.

Weakness and pallor due to fever and anemia are almost the rule and there are very few who, on careful questioning, do not admit the presence of the former symptom.

While most patients complain of weakness or some lesion of the mouth as a first symptom, there are some who complain of adenopathy, dyspnoea, edema of the feet, skin lesions, or gastro-intestinal disturbances. Forkner (66) has given a particularly fine description of the physical signs and symptoms. He calls attention to the prevalence of mouth lesions, the size of the spleen (between that of lymphatic and that of myelogenous leukemia) and the usual limitation of enlarged lymph nodes to the cervical region. From what has already been said of the extreme variation in signs and symptoms it must be evident that, while these clinical findings are always of great importance and may serve to separate the typical case of monocytic leukemia from typical cases of the other leukemias, there are many instances in which the diagnosis can be made only after exhausting all possible diagnostic procedures.

Fever is usually high in the acute type of the disease and lasts throughout its course. Anemia and exhaustion develop rapidly and frequently early. Pneumonia, bleeding, heart failure, and other incidents have been found terminally.

So far no authenticated instance of recovery has been reported and the prognosis is always grave with eventual fatality as the outcome.

In the typical acute case of monocytic leukemia there is a prodromal period of weakness and malaise. This is short in duration and followed usually by abrupt onset of gingivitis, painful teeth, bleeding gums, sore throat, or any combination of these symptoms. Gastro-intestinal symptoms may be described and occasionally a history of dysuria or hematuria is given. On examination the patient is found to be extremely ill, is prostrated and pallid, and is found to have a high fever and tachycardia. Hemorrhagic areas in the skin are extremely common. In the acute form of the disease the gums show proliferative, ulcerated lesions, or there may be angina with a dirty gray membrane in others. The lymph nodes of the neck are frequently large and tender under these circumstances. The other lymph nodes are frequently not involved. The lungs are not involved as part of the disease, although secondary infections are seen. The heart rate is rapid, and if anemia has progressed, there is often a hemicystolic murmur. The spleen is moderately enlarged and the liver is usually palpable. The course is febrile, the patient becoming more pallid and prostrated, and death ensues in a few days unless the acute episode is relieved by remission. Pneumonia infections in various areas of the body, and hemorrhages in many of the organs, together with invasion of any of the organs by the type cell is found terminally.

Quite different is the picture in the chronic case or in those patients who are seen during remission. In these instances the symptoms are minimal, the patient frequently complaining only of some weakness, loss of energy and malaise.

and monocyte count but there is rarely any difficulty in diagnosis. Subacute bacterial endocarditis may be ruled out by the absence of blood stream infection and the presence of a monocytic blood picture. These two entities are very much alike clinically since with both are associated petechiae, heart murmurs (hemic in leukemia), splenomegaly and extreme illness. Typhoid fever, undulant fever and yeast infections may prove confusing but all can be ruled out by the appropriate laboratory tests and by the course of the disease.

While the peripheral blood of infectious mononucleosis may have certain superficial similarity to that of monocytic leukemia, careful study of the blood films—particularly supra-vital preparations—will serve to distinguish between the two. In the latter technique it becomes obvious that the cells of infectious mononucleosis are really of the lymphocytic series. In addition the Paul-Bunnell Test is negative in leukemia. Both Israels (105) and Downey (44) have discussed this differential diagnosis at length.

In certain cases of monocytic leukemia agranulocytosis has been present to a marked degree. If the patient is seen only at this time the blood films may present a completely agranulocytic appearance and the clinical picture may be so typical that a diagnosis of malignant neutropenia may be made. Thus one of the cases observed by Klumpp and Evans became completely agranulocytic in the terminal days of her illness. If the course of the disease can be studied, as was the case with Klumpp and Evans, no such confusion arises but otherwise final diagnosis may have to be made after biopsy or autopsy.

The presence of large numbers of purpuric hemorrhages and the thrombocytopenia which are characteristic of this form of leukemia may lead to difficulty in diagnosis from thrombocytopenic purpura. However, in the latter disease there is no monocytosis and no immature monocytes are seen in the blood.

In certain instances Hodgkin's Disease may closely resemble monocytic leukemia. In fact Osgood (166) states that the chronic aleukemic form of the disease may be identical with Hodgkin's disease. Lymph node biopsy may show similar structure with marked eosinophilia in both diseases. Under these circumstances fixed and supra-vital studies of the blood and bone marrow are found to be the best differential procedure.

As has already been mentioned the most difficult differential diagnosis lies between monocytic and the other types of leukemia. When there is a preponderance of "blast cells" with very few adult cells of any series this diagnosis may be practically impossible in the fixed spread. If there is opportunity to study the individual over a considerable period of time spreads will nearly always be found in which adult cells of one or the other strain are demonstrable and it is always helpful to remember that a blast "is known by the mature cells whose company it keeps" (Klumpp (254)). The peroxidase stain is helpful in differentiating lymphocytes from both monocytes and myelocytes as the latter two strains both take the stain whereas the lymphocytes do not. Experienced observers can usually distinguish between the staining of myelocytes and monocytes by the peroxidase stain—the myelocytes having more and deeper staining granules. Supra-vital examination of the blood and bone marrow is of great

of nine months During the first observations the leukocyte count was high with 95 per cent of the cells in the myelocytic series This myelocytic preponderance was maintained for five months when the picture changed markedly and, at the end of six months, the differential count showed a percentage of 91 of the monocytic series Since no cells of the reticulo-endothelial type were seen at any time in the circulating blood they conclude that in this instance the monocytes stemmed from the myeloblast, that this is a variant of myelogenous leukemia, and it comes under the classification of Downey's "Naegeli leukemia" Occasionally the reverse also happens in the course of a perfectly typical case of monocytic leukemia a shower of myelocytes may cause the blood to appear very much like that of myelocytic leukemia (Dameshek's (38) second case) It is these situations which probably give rise to those cases reported as "mixed leukemia,") though it is theoretically possible that two or even all three types could co-exist

It is in the aleukemic cases that difficulties in diagnosis become most acute However, with supra-vital technique, peroxidase stain and bone marrow studies, the diagnosis can usually be made, and can be confirmed by autopsy or occasionally by biopsy In most of these cases there are qualitative changes in the monocytes which can be clearly demonstrated in vivo but in some diagnosis has to wait for tissue examination

Diagnosis of the chronic cases is not difficult if there are large numbers of adult monocytes in the blood together with a few immature cells What has already been said of the criteria for diagnosis of the acute form of the disease applies also in this connection However, in those chronic cases where the circulating blood is aleukemic, the diagnosis is very difficult In the chronic case without leukemic blood, the cells are only slightly different from normal In the fixed stain these *minimal differences are not* very evident In the supra-vital studies the following variations are found, (1) the lymphocyte-monocyte ratio is reversed, (2) a few young monocytes with more granular cytoplasm and round or oval nuclei, and (3) the young cells of the monocyte series can be identified by their *red staining vacuoles and green mitochondria* whereas in the fixed spread these cells may appear to belong to one of the other series Final diagnosis in this type of case sometimes rests upon biopsy, postmortem examination, or both

DIFFERENTIAL DIAGNOSIS

There are a number of infections from which the differential diagnosis of monocytic leukemia must be made Inversion of the lymphocyte-monocyte ratio may occur in some of these and there may be a very considerable number of monocytes circulating in the blood Thus from tuberculosis the diagnosis is made, on the one hand, by the absence of demonstrable lung disease and the absence of tubercle bacilli, and, on the other hand, by the presence of the stigmata of monocytic leukemia Sometimes the removal of a lymph node for study will settle the problem Syphilis can usually be excluded by the absence of a positive Wasserman reaction though the skin lesions are sometimes very similar in the two diseases In whooping cough there is sometimes a rather high lymphocyte

and monocyte count, but there is rarely any difficulty in diagnosis. Subacute bacterial endocarditis may be ruled out by the absence of blood stream infection and the presence of a monocytic blood picture. These two entities are very much alike clinically since with both are associated petechiae, heart murmurs (hemic in leukemia), splenomegaly and extreme illness. Typhoid fever, undulant fever and yeast infections may prove confusing but all can be ruled out by the appropriate laboratory tests and by the course of the disease.

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benefit in separating the monocytic from the other strains of cells. The typical vacuolar rosette is not seen in myelocytes and lymphocytes and the size and structure of the cells appear very unlike in the three series. In the one instance the bone marrow is hyperplastic and in the other it is hypoplastic.

In general it may be repeated that the diagnosis of monocytic leukemia is always difficult, that all means available for diagnosis should be used, that the cases should be studied over as long a time period as possible and finally that controversy is very apt to arise as soon as the disease is mentioned. History, physical examination, peripheral blood counts and spreads examined with fixed cell technique are all of immense value and may serve to make the diagnosis seem very likely but the use of supra-vital staining adds greatly to the evidence. Bone marrow studies and biopsy of lymph nodes offer still further convincing evidence of the disease and whatever doubt is left after all these studies are completed is finally removed by autopsy.

Beck, Dameshek, and Doan all call attention to the fact that diagnosis is usually possible without autopsy.

TREATMENT

In the acute form of monocytic leukemia no treatment has proved to be of value. Transfusion has been widely used and has served to keep the patient alive for a short time. Occasionally a remission has been described following transfusion but it seems probable that in such instances the transfusion is not the causative factor. X-ray has proved of little or no value. Various preparations of arsenic have been used without success as have various liver extracts. X-ray of the spleen and even splenectomy have been performed, but in the cases where success has been claimed for either measure there seems to have been considerable doubt as to the diagnosis. Theoretically at least, splenectomy is contra-indicated in leukemia since it is in the spleen that excess of white blood cells is controlled by lysis and sequestration.

In the chronic form of monocytic leukemia X-ray has been reported to have a beneficial effect. Some interesting work has been done by Dean and Wiseman (237, 43, 271) on the relationship of chronic monocytic leukemia to disordered fat metabolism. While this work has not yet progressed to the point of proof, they feel hopeful that eventually control of the fat metabolism may prove beneficial in treatment of this form of the disease.

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- 266 SYDENSTRICKER, V, Georgia
- 267 TALBOTT J, Massachusetts
- 268 THOMPSON W New York
- 269 WATKINS, C, Minnesota
- 270 WISMAN, B, Ohio

APPENDIX

Because a number of the answers to the questionnaire which was sent out in July 1941, were in great detail and because of their interesting points of view I take pleasure in quoting directly from some of these men, the quotations being authorized personally by the authorities who are quoted

DR HAL DOWNNEY It seems to me that much of the confusion regarding monocytic leukemia is due to the fact that many authors assume that any cell derived from the reticulum and getting into the blood must necessarily be a "monoblast" regardless of whether or not the blood smears contain monocytes. I do not designate any case a monocytic leukemia unless the blood smears contain many genuine monocytes and their precursors. In other cases the young monocytes can be traced to cells that have originated in the reticulum and the organs often show the reticular hyperplasia. I have called such cases monocytic leukemia of Schilling type because Schilling believes that all monocytes are derived from the reticulum

DR GEORGE FARRAR. For the time being I like to call the whole group reticulo-endotheliosis just as I group the other leukemias under myelosis and lymphomas. I also believe that there is a monocytic myeloblast (a monocyte-like cell that differs from the cytology of the reticulo-endotheliosis case) and, furthermore, that the clinical course differs from that of the reticulo-endotheliosis in resembling more that of myelogenous leukemia

DR RAPHAEL ISAACS There is unquestionably a monocytic leukemia. In it, the pre-dominant cell in the blood is the monocyte with immature bone marrow cells of other types crowded out from the marrow. It is to be differentiated from the type of chronic myelogenous (poly neutrophile) leukemia, in which some immature monocytes are crowded out of the bone marrow into the blood. As leukemia goes, the monocytic type is relatively common having previously been grouped with myelogenous leukemia

DR FOR P KRACKE I believe that there are two types of monocytic leukemia, one is the disease characterized by proliferation of the reticulo-endothelial elements and probably could be called reticulo-endotheliosis and the second is monocytic leukemia in which the disease is a variant of the myelogenous type. I have definitely seen two cases in which the excessive circulating leukocytes could in no way be differentiated from monocytes. In one of these the process monocytes later became a typical myelogenous leukemia and in the other the autopsy findings showed infiltration of organs with

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PERSONAL COMMUNICATIONS

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|----------------------------|---------------------------------|
| 231 BASSLER, A , New York | 234 CLOUGH, P , Maryland |
| 232 BECK, R , Virginia | 235 CUNNINGHAM, R , California |
| 233 BLAKE, F , Connecticut | 236 DAVESHEK, W , Massachusetts |

